Short Communication

Association between Insulin-Like Growth Factor-I:Insulin-Like Growth Factor-Binding Protein-1 Ratio and Metabolic and Anthropometric Factors in Men and Women

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Abstract

Several prospective observational studies have suggested that elevated circulating IGF-I levels are associated with an increased risk of cancer. These observations may provide a potential mechanism through which previously identified metabolic and anthropometric factors, such as obesity and elevated insulin and glucose levels, may operate. We therefore examined metabolic and anthropometric influences on circulating levels of insulin-like growth factor-I (IGF-I), insulin-like growth factor-binding protein-1 (IGFBP-1), and the IGF-I:IGFBP-1 ratio in a middle-aged population of 349 men and 492 women. IGF-I showed only modest inverse associations with indices of adiposity. However, we found that low IGFBP-I levels and an increased IGF-I:IGFBP-1 ratio were strongly associated with increased levels of insulin and glucose in men and women. Body mass index was also positively related to the IGF-I:IGFBP-1 ratio in men ($P < 0.001$) and women ($P < 0.001$), independent of metabolic correlates of IGFBP-1 and IGF-I. Similarly, waist:hip ratio and waist circumference were also associated with an increased IGF-I:IGFBP-1 ratio and low circulating IGFBP-1 levels. These findings suggest that individuals with greater fat mass and upper body obesity may have elevated levels of bioavailable or free IGF-I, which could, in part, mediate the reported associations among metabolic and anthropometric factors and cancer risk.

Introduction

Several prospective observational studies have shown that circulating insulin-like growth factor-I (IGF-I) levels are positively associated with risk of several cancers, suggesting that IGF-I may be important in the pathophysiological processes underlying carcinogenesis (1, 2). These observations may provide a potential mechanism through which previously identified metabolic and anthropometric factors, such as obesity and elevated insulin and glucose levels, may operate to increase risk of cancer (3–9).

Specifically, obesity, hyperinsulinemia, and hyperglycemia may be associated with increased levels of circulating bioactive or free IGF-I (3–5, 10, 11). However, population-based studies have found conflicting associations among markers of IGF-I bioavailability, indices of adiposity, and metabolic factors (12–19). Many of these studies have used the IGF-I:insulin-like growth factor-binding protein-1 (IGFBP-3) molar ratio as a surrogate marker of IGF-I bioavailability. Both IGF-I and IGFBP-3 are regulated predominantly by growth hormone (10). However, fewer epidemiological studies have examined the associations among metabolic and anthropometric factors and IGFBP-1, an acute mediator of IGF-I bioavailability that is inversely regulated by insulin (20).

We therefore examined the association among anthropometric and metabolic factors and circulating levels of IGF-I and IGFBP-1 in a population of middle-aged men and women. In particular, because hepatic IGFBP-1 production is acutely suppressed by insulin and hyperinsulinemia is associated with obesity, we aimed to determine whether a higher IGF-I:IGFBP-1 ratio is associated with increased adiposity and elevated levels of glucose and insulin.

Materials and Methods

Participants and Protocol. The volunteers in this study were all participants in the Ely Study, a continuing population-based cohort study in Ely, Cambridgeshire, United Kingdom. The detailed design of the study has been described previously (21). The original sample, comprising 1122 people without known diabetes, was recruited between 1990 and 1992 at random from a population-based sampling frame consisting of all people in Ely between 40 and 65 years of age in 1990. The initial response rate was 74%. These individuals attended a morning clinic and underwent a standard 75-g oral glucose load, having fasted since 10:00 p.m. the previous evening.

Inclusion Criteria. Of the 1122 people in the study, 82 (7.3%) had undiagnosed type 2 diabetes (a fasting plasma glucose value $\geq$7.0 mM or a 2-h plasma glucose value $\geq$11.1 mM) at the baseline examination, according to current WHO criteria (22). To assess the determinants of circulating IGFs in a healthy population and because type 2 diabetes may influence IGF levels (23), we excluded these 82 participants from the analysis. Of the remaining 1040 participants, 841 (81%) had blood available for assessment of baseline fasting IGF-I and IGFBP-1 concentrations. Mean fasting glucose ($P = 0.587$), 2-h glucose ($P = 0.296$), body mass index (BMI; $P = 0.230$), age ($P =$

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Table 1 Characteristics of the study participants, the Ely Study, 1990–1992

Data shown are means and 95% confidence intervals where applicable, unless otherwise indicated.

	Men (n = 349)	Women (n = 492)	P
Age (years)	54.2 (53.4–55.0)	53.3 (52.6–54.0)	0.102
Obese[a] (%)	38 (11)	78 (16)	0.040
Former/current smokers[c] (%)	208 (64)	194 (40)	<0.001
Antihypertensive medication (%)	53 (15)	66 (13)	0.468
Height (cm)	175 (174–176)	162 (161–163)	<0.001
Body mass index (kg/m^2)	25.9 (25.5–26.3)	25.6 (25.2–26.0)	0.253
Waist:hip ratio	0.90 (0.90–0.91)	0.76 (0.76–0.77)	<0.001
Waist circumference (cm)	91 (90–92)	78 (77–79)	<0.001
Glucose at 2 h[b] (mmol/l)	5.9 (5.8–6.1)	6.1 (6.0–6.2)	0.098
Insulin at 0 h[b] (pmol/l)	40 (38–42)	39 (37–42)	0.547
IGF-I at 0 h[b,c] (ng/ml)	159 (153–165)	138 (134–143)	<0.001
IGFBP-1 at 0 h[c] (ng/ml)	19 (18–20)	26 (25–28)	<0.001
IGF-I/IGFBP-1 ratio[c]	8.4 (7.7–9.2)	5.2 (4.9–5.7)	<0.001

[a] Obese = body mass index ≥30 kg/m^2.
[b] Geometric means and 95% confidence intervals.
[c] IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein.

0.478), and the proportion of current/former smokers (P = 0.880) did not differ between individuals in this analysis and the 199 participants who did not have blood available for IGF assays. The study population for this investigation therefore comprised 349 men and 492 women.

Anthropometric and Metabolic Assessment. At the clinic visit, height and weight were measured with the participant in light clothing. BMI was estimated as weight (kg) divided by height (m) squared. Waist and hip circumferences were measured in duplicate with a fabric tape. Blood samples were taken at fasting and 120 min after a 75-g oral glucose load. All samples were permanently stored at −70°C within 4 h. Plasma glucose was measured in the routine National Health Service Laboratory at Addenbrooke's Hospital by the hexokinase method (24). Plasma insulin was measured by two-site immunometric assays with either ^{125}I or alkaline phosphatase labels (25, 26). Cross-reactivity with intact proinsulin was <0.2% and interassay coefficients of variation were <7%. Levels of IGF-I and total IGFBP-I (using monoclonal antibody 6303, which detects all IGFBP-1 phosphoforms) were determined by previously reported antibody-based assays (27–29). The assays have respective detection limits of 28 ng/ml and 3 μg/l and within- and between-assay coefficients of variation <10%. The Cambridge Local Research Ethics Committee, United Kingdom, granted ethical permission for the study, and informed consent was obtained from all participants.

Statistical Analysis. To obtain near-normal distributions, we applied logarithmic transformations to all nonnormally distributed variables. For descriptive analyses, we used t tests and standard χ^2 tests to compare means and proportions of characteristics between men and women. Spearman correlation coefficients were used to assess simple associations among continuous variables of interest and concentrations of circulating IGFs. We used multivariate linear regression analysis to assess independent associations among IGF-I and IGFBP-1 and metabolic and anthropometric factors. Linear trends comparing continuous variables with their corresponding categorical (quartiles) or polynomial terms and possible interactions between covariates and IGFs were assessed with log-likelihood ratio tests. All data are presented for men and women separately. All analyses were done with Stata 7.0 statistical package (Stata Corp., TX).

Results

Demographic Factors. Characteristics of the study participants are shown separately for men and women in Table 1. Mean IGF-I levels were significantly higher in men, whereas mean IGFBP-1 levels were higher in women. IGF-I was inversely correlated with age in both men ($r = -0.21$; $P < 0.001$) and women ($r = -0.29$; $P < 0.001$). By contrast, IGFBP-1 was positively correlated with age in men ($r = 0.11$; $P = 0.04$) and women ($r = 0.13$; $P = 0.002$). However, levels of IGF-I and IGFBP-1 did not differ by smoking status or use of antihypertensive medication in men or women (data not shown).

Metabolic Factors. The associations among IGF-I, IGFBP-1, the IGF-I:IGFBP-1 ratio, and metabolic factors are shown in Table 2. In multivariate analysis, IGF-I was inversely related to age and IGFBP-1 in men and women. However, IGF-I showed no linear association with insulin or glucose levels. By contrast, IGFBP-1 showed strong inverse associations with both insulin and glucose in men and women. As a result, there was a positive association between the IGF-I:IGFBP-1 ratio and insulin and glucose levels (Table 2).

Anthropometric Factors. The age-adjusted associations among IGF-I, IGFBP-1, the IGF-I:IGFBP-1 ratio and anthropometric variables for men and women are shown in Table 3. In age-adjusted analysis, IGF-I was unrelated to anthropometric

Table 2 Multivariate-adjusted associations among IGF-I,[a] IGFBP-1, the IGF-I/IGFBP-1 ratio and metabolic variables for 349 men and 492 women, the Ely Study, 1990–1992

All variables were added simultaneously.

Variable	IGF-I[b]		IGFBP-1[b]		IGF-I:IGFBP-1 ratio[b]	
	β[c]	SE[c]	β	SE	β	SE
Men						
Age (years)	−0.007[d]	0.002	0.012[d]	0.004	−0.024[e]	0.005
BMI (kg/m^2)	−0.012	0.007	−0.062[e]	0.011	0.055[e]	0.014
Glucose at 2 h[b] (mmol/l)	−0.114	0.084	−0.283[f]	0.128	0.186	0.162
Insulin at 0 h[b] (pmol/l)	0.012	0.041	−0.572[e]	0.062	0.671[e]	0.078
IGF-I at 0 h[b] (ng/ml)			−0.305[d]	0.090		
IGFBP-1 at 0 h[b] (ng/ml)	−0.11[d]	0.031				
Women						
Age (years)	−0.013[e]	0.002	0.012[e]	0.003	−0.030[e]	0.004
BMI (kg/m^2)	−0.012[d]	0.004	−0.044[e]	0.006	0.034[e]	0.008
Glucose at 2 h[b] (mmol/l)	−0.044	0.073	−0.319[d]	0.110	0.414	0.141
Insulin at 0 h[b] (pmol/l)	0.031	0.036	−0.372[e]	0.051	0.380[e]	0.066
IGF-I at 0 h[b] (ng/ml)			−0.223[d]	0.067		
IGFBP-1 at 0 h[b] (ng/ml)	−0.10[d]	0.030				

[a] IGFBP, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; BMI, body mass index.
[b] Natural log transformed.
[c] β and SE, regression coefficient and SE for mean change in IGF variable for each unit increase in the independent variable.
[d] $P < 0.01$.
[e] $P < 0.001$.
[f] $P < 0.05$.

indices in both men and women. However, IGFBP-1 showed strong inverse associations, and IGF-I:IGFBP-1 showed strong positive associations with BMI, waist circumference, and waist:hip ratio.

In a multivariate model adjusting for correlates of IGF-I in Table 2 (age and IGFBP-1), IGF-I was inversely associated with BMI [β (SE) = −0.012 (0.007); P = 0.069], waist circumference [β (SE) = −0.007 (0.002); P = 0.001], and waist:hip ratio [β (SE) = −0.964 (0.337); P = 0.004] in men. After adjustment for age and IGFBP-1, IGF-I was also inversely associated with BMI [β (SE) = −0.013 (0.004); P = 0.001] and waist circumference [β (SE) = −0.006 (0.002); P = 0.001] in women. However, adjusting for correlates of IGFBP-1 and IGF-I:IGFBP-1, including fasting insulin and 2-h glucose concentrations, did not materially alter the associations among IGFBP-1, IGF-I:IGFBP-1, and indices of adiposity in men or women.

Additional analyses comparing categorical anthropometric variables with their corresponding linear terms showed no statistically significant evidence for nonlinearity with IGF-I, IGFBP-1, and IGF-I:IGFBP-1 values in men. There was also no evidence of nonlinearity between IGFBP-1 or IGF-I:IGFBP-1 and indices of adiposity in women. However, the associations among IGF-I, BMI, and waist:hip ratio showed nonlinear associations with IGF-I in women (Table 4). Adding a categorical term for BMI significantly improved the fit of the model for IGF-I adjusted for age and IGFBP-1 [χ^2 (3 df) = 11.00; P = 0.012] and showed a statistically significant nonlinear association [χ^2 (2 df) = 7.96; P = 0.019]. Similarly, a categorical term for waist:hip ratio improved the fit of the model for IGF-I adjusted for age and IGFBP-1 [χ^2 (3 df) = 10.51; P = 0.015]. Again this relation was nonlinear [χ^2 (2 df) = 9.17; P = 0.010].

Discussion

In this population of middle-aged men and women, we found that low IGFBP-I levels and an increased IGF-I:IGFBP-1 ratio were associated with increased levels of insulin and glucose. Relatively high BMI, waist:hip ratio, and waist circumference were also associated with an increased IGF-I:IGFBP-1 ratio and low IGFBP-1 levels in men and women. These findings suggest that individuals with elevated levels of glucose and insulin, greater fat mass, and upper body obesity may have higher levels of bioavailable or free IGF-I (30).

The limitations of this study warrant some discussion. It is possible that unidentified correlates of IGF-I and IGFBP-1 could explain or modify our observations. Lack of data on other potential confounders and effect modifiers may also alter the associations reported in this study. For example, we had no measures of menopausal status in this study. Earlier studies have reported that menopausal status may influence IGF levels, reflecting changes in circulating estrogen (17, 19). Similarly, adjustment for other IGFBPs may have altered the results reported here. However, the principal IGFBP, IGFBP-3, has previously shown conflicting associations with anthropometric and metabolic indices, either showing no relationship (14, 16) or positive associations (15, 17, 31).

Reproducibility of IGF-I and IGFBP-1 is relatively high (r = 0.6–0.9; Ref. 32). Nevertheless, measurement error as a result of variability in levels of these hormones and other biological variables might have led to underestimation of the associations among IGF-I, IGFBP-1, and metabolic and anthropometric factors, and thus to residual confounding. However, the IGFs showed the expected associations with age and gender (10, 33). Furthermore, all IGF-I and IGFBP-1 measurements were taken from fasting blood samples in the morning; therefore, variability as a result of changes in circulating insulin and nutritional determinants is probably marginal (34).

Previous investigations of the relationship between IGF-I levels and indices of adiposity and relative body size have reported inconsistent findings (12–19, 31). In the present study, we found that BMI was inversely associated with IGF-I levels in men and women. However, this relationship was statistically significant only after adjusting for IGFBP-1, suggesting that IGFBP-1 confounds or modifies the association. Our data suggest that the inverse association between IGF-I and BMI is stronger in participants with low IGFBP-1 levels. These individuals are generally characterized by insulin resistance and obesity. Speculatively, this observation may reflect differences in IGF-I bioavailability. However, given the complexity of IGF-I regulation and the interrelations among IGF-I, insulin, and growth hormone, which may all influence body weight regulation, this interpretation may be overly simplistic and is unlikely to be confirmed in an epidemiological investigation.

Nevertheless, significant inverse associations between

Table 3 Age-adjusted associations among IGF-I,[a] IGFBP-1, the IGF-I/IGFBP-1 ratio and anthropometric variables for 349 men and 492 women, the Ely Study, 1990–1992

Bivariate linear regression analysis.

Variable	IGF-I[b]		IGFBP-1[b]		IGF-I:IGFBP-1 ratio[b]	
	β[c]	SE[c]	β	SE	β	SE
Men						
Height (cm)	−0.001	0.003	−0.011	0.007	0.010	0.008
BMI (kg/m^2)	−0.001	0.006	−0.110[d]	0.012	0.105[d]	0.014
Waist (cm)	−0.003	0.002	−0.040[d]	0.004	0.033[d]	0.005
Waist:hip ratio	−0.465	0.322	−4.523[d]	0.640	4.059[d]	0.777
Women						
Height (cm)	0.001	0.003	−0.002	0.005	0.002	0.006
BMI (kg/m^2)	−0.006	0.004	−0.069[d]	0.006	0.062[d]	0.007
Waist (cm)	−0.003	0.002	−0.033[d]	0.002	0.030[d]	0.003
Waist:hip ratio	−0.121	0.304	−4.424[d]	0.510	4.303[d]	0.301

[a] IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; BMI, body mass index.
[b] Natural log transformed.
[c] β and SE, regression coefficient and SE for mean change in IGF variable for each unit increase in the independent variable.
[d] $P < 0.001$.

Table 4 Mean levels of IGF-I[a] according to quartiles of BMI and waist:hip ratio for 491 women, the Ely Study, 1990–1992

All data are adjusted for age and insulin-like growth factor-binding protein-1.

Quartiles	n	IGF-I[b] (ng/ml)
BMI (kg/m^2)		
<22.6	123	138 (129–148)
22.6–24.4	123	145 (136–155)
24.5–27.7	123	144 (135–153)
>27.7	122	125 (117–134)
Waist:hip ratio		
<0.72	123	137 (128–146)
0.72–0.75	123	142 (133–151)
0.76–0.80	123	147 (138–157)
>0.80	122	127 (119–136)

[a] IGF, insulin-like growth factor; BMI, body mass index.
[b] Results are natural log transformed and given as geometric means and 95% confidence intervals.

IGF-I levels and BMI have been reported in earlier studies (35–37). By contrast, investigations have also shown significant positive associations between IGF-I levels and BMI in Japanese and Chinese men (15, 38). We also found that, after adjustment for IGFBP-1, IGF-I showed an inverse association with waist:hip ratio and waist circumference in men and with waist circumference in women. There was also a suggestion that the associations among IGF-I, BMI, and waist:hip ratio were nonlinear in women. Although the latter is consistent with a previous study (12), earlier reports are inconclusive, having found both inverse and null associations (18, 31, 39–43).

At least four studies have assessed the association between IGF-I levels and distribution of visceral adipose tissue based on computed tomography scans. Three of these investigations found that IGF-I levels were inversely associated with visceral adipose tissue in overweight or obese men and women (40–42), whereas a more recent study found no significant associations between visceral adiposity and IGF-I levels in men and women (14). One of these reports also found that changes in IGF-I levels were inversely related to changes in visceral fat after physical activity intervention (42).

Collectively, findings from reports examining the relationships among IGF-I, BMI, and related measures of adiposity suggest that these associations may vary among populations with different BMI ranges (12, 15, 36). Thus, populations with a generally low BMI (*e.g.*, BMI < 25 kg/m^2) may exhibit positive associations between IGF-I levels and BMI. Conversely, populations that tend to be overweight or obese (BMI > 25 kg/m^2) may show inverse associations between IGF-I and BMI (36). Indeed, some investigations have shown suggestive evidence for this nonlinear association (12, 17, 36), but not all (15).

However, the underlying biological mechanisms for these nonlinear or divergent findings are unclear. Obesity is associated with decreased levels of circulating growth hormone (GH), which is the main positive regulator of hepatic IGF-I production (10). Lower GH is thought to be attributable to increased free IGF-I levels as a result of the insulin-mediated suppression of IGFBP-1 and possibly IGFBP-2 (23). Thus, one may expect lower levels of circulating IGF-I in obese individuals. Moreover, GH deficiency in humans is associated with the accumulation of visceral adipose tissue and decreases in lean body mass (44). However, the elevated levels of circulating insulin seen in people with obesity and insulin resistance also increase hepatic GH sensitivity by up-regulating GH receptor levels and thereby increasing GH-regulated production of hepatic IGF-I (23, 45). The relative magnitude of these two opposing effects of insulin on hepatic IGF-I production may therefore be the main determinant of IGF-I levels in conditions associated with hyperinsulinemia, such as obesity. Thus differences in the complex processes regulating IGF-I expression and activity may explain why the association between IGF-I and indices of adiposity and relative body size may be nonlinear (12, 36).

As expected, IGFBP-1 levels were significantly lower in men and women with higher BMIs, waist:hip ratios, and waist circumferences. In turn, the mean IGF-I:IGFBP-1 ratio was greater in people with higher BMIs, waist:hip ratios, and larger waist circumferences. In accordance with these findings, three recent cross-sectional studies in women and in an elderly Finnish population have shown that IGFBP-1 levels are inversely associated with BMI and hyperinsulinemia (31, 43, 46).

However, most population-based studies have focused on the IGF-I:IGFBP-3 ratio and its association with anthropometric measures and have generally found conflicting associations (14, 17). By contrast, several small clinical investigations and experimental studies have consistently reported decreased IGFBP-1 levels in people with obesity or elevated insulin levels (20, 23, 30, 47). Furthermore, because hepatic production of IGFBP-1 is acutely suppressed by insulin (20), IGFBP-1 is thought to be a dynamic regulator of circulating bioavailable IGF-I *in vivo*, forming the link between nutrition and growth (10).

On a molar basis, IGFBP-1 constitutes only a small percentage of the total pool of circulating IGFBPs, whereas IGFBP-3 is the major binding protein in the circulation (11). However, experimental and clinical studies have suggested that IGFBP-1 is a primary regulator of "free," readily dissociable, or bioactive IGF-I (47, 48). An investigation using a recently developed immunoassay for the IGF-I–IGFBP-1 binary complex showed that there was a close inverse association between IGFBP-1 and free IGF-I (49) Thus, chronically elevated levels of bioavailable IGF-I, as a result of reduced IGFBP-1 levels in conditions associated with hyperinsulinemia, may promote the survival of transformed and abnormal cells that would normally undergo apoptosis (50). IGF-I is a potent antiapoptotic and mitogenic factor for many cell types (1). As a result, it is possible that the insulin-related changes in IGF-I bioavailability could, in part, mediate the reported associations between metabolic and anthropometric factors and cancer risk (3, 5).

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