Lack of Association between Adipose Tissue Distribution and IGF-1 and IGFBP-3 in Men and Women[1]

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Abstract

Insulin, insulin-like growth factor-1 (IGF-1), IGF binding protein-3 (IGFBP-3), and obesity, and in particular visceral obesity, are putative cancer risk factors. Little is known, however, about the relationship between IGFs and obesity. We investigated the relationship between adipose tissue distribution and IGF-1 and IGFBP-3. Single-slice abdominal computed tomography scanning through the L4-L5 interspace was used to measure visceral adipose tissue (VAT) and subcutaneous adipose tissue (SQAT) in 432 community-based subjects (267 men, 165 women; ages, 55–77), participating in a cancer screening trial. Insulin, IGF-1, IGFBP-3, and the ratio of IGF-1:IGFBP-3, measured by radioimmunoassay, were compared with age, body mass index, absolute and relative VAT and SQAT, and total abdominal fat. We found that men had a higher mean IGF-1 (129.5 *versus* 108.9 ng/ml; $P < 0.0001$) and more VAT (201.5 cm^3 *versus* 166.6 cm^3; $P < 0.0001$) than women. In men and women, there was no correlation between IGF-1, IGFBP-3, or the ratio of IGF-1:IGFBP-3 with body mass index, total fat, VAT or SQAT, or fasting insulin. In contrast, fasting insulin was highly correlated to all measures of obesity ($P = 0.0001$). We conclude that obesity, adipose tissue distribution, and in particular VAT are not correlated with IGF-1, IGFBP-3, or the molar ratio of IGF-1:IGFBP-3. The lack of association between obesity and the IGF-1 axis suggests that the IGF-1 axis is not a likely mediator between VAT and disease.

Introduction

IGFs[3] and IGFBPs have important roles in cell cycle regulation and possess mitogenic and antiapoptotic properties (1). Research has focused on the relationship of IGFs and IGFBPs, principally IGF-1 and IGFBP-3, to a variety of tumors including colorectal (2–4), prostate (5–7), breast (8), and lung cancer (9). The combination of a high circulating level of free IGF-1 and/or a low IGFBP-3 has been associated with an increased risk of cancer.

There are at least two distinct IGFs (IGF-l and -II) and six different high-affinity IGFBPs (1, 10). Seventy-five % of IGF-1 is bound to IGFBP-3, more than 20% is bound to other high-affinity IGFBPs of lower molecular weight, and less than 5% is considered "free" in the circulation. IGFBP-3, either through binding IGF-1 or by acting through an independent cell surface receptor, can oppose or enhance the biological action of IGF-1 (10).

Relatively little is known about the regulatory determinants of IGF-1. Growth hormone is the primary regulator of IGF-1 synthesis in the liver (10). However, autocrine and paracrine production of IGF-1 may be as important as, or more significant than, hepatic release. It is unknown whether the higher levels of IGF-1 observed in patients with cancer originate from enhanced growth hormone secretion or are a result of local and/or autocrine-paracrine production with subsequent entry into the systemic circulation.

Reduced levels of IGF-1 have been associated with aging (11) and in one study, with African-American race (12). Variation in IGF-1 levels with the menstrual cycle and with oral contraceptive use have also been reported (13). Obesity can affect the secretion of growth hormone, which would in turn affect the secretion of IGF-1 by the liver. However, IGF-1 levels in obesity have been reported to be high, normal, or reduced (14). Further exploration of the relationship between obesity and IGF-1 is warranted because both obesity and IGF-1 have been associated with cancer. For example, BMI (15–17) and in particular VAT (16, 18) have been linked to colorectal cancer, and so have insulin, IGF-1, and IGFBP-3 (2–4, 19). Insulin and IGFs can stimulate cell proliferation in the colonic mucosa and in carcinoma cell lines, and affect apoptosis (20–22). Two recent cohort studies demonstrate a strong association between insulin and the subsequent development of colorectal cancer (3, 19).

VAT is a determinant of insulin resistance and is associated with hyperinsulinemia and elevated triglyceride levels (23–26). If it were demonstrated that increased visceral adiposity was associated with a higher level of IGF-1, then, in addition to the insulin pathway, an additional pathway between abdominal obesity and colon carcinogenesis would be established.

In this investigation, the association between adipose tissue distribution and IGF-1 and IGFBP-3 is examined in a large, community-based sample. A better understanding of the factors that impact on the IGF-1 axis will enhance understanding of its role in disease and could be used to identify strategies for intervention.

Materials and Methods

Population. The subjects in this study were drawn from enrollees in the Pittsburgh site of the Prostate, Lung, Colorectal,

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[3] The abbreviations used are: IGF, insulin-like growth factor; IGFBP, IGF-binding protein; VAT, visceral adipose tissue; SQAT, subcutaneous adipose tissue; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer (screening trial); CT, computed tomography; BMI, body mass index; CI, confidence interval.

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and Ovarian Cancer (PLCO) screening trial, a multicenter randomized clinical trial evaluating the effect of cancer screening tests on site-specific cancer mortality (27). Subjects in the intervention arm of the trial undergo periodic cancer screening tests including chest X-ray, flexible sigmoidoscopy, and for men, digital rectal exam and prostate-specific antigen test, and for women, CA-125 test and vaginal ultrasound. Subjects were recruited into the PLCO trial through mass mailings. Participants in the PLCO trial met the following eligibility criteria: (*a*) age, 55–74; (*b*) not currently undergoing treatment for cancer except for basal cell or squamous cell skin cancer; (*c*) no known prior cancer of the colon, rectum, prostate, lung, or ovaries; (*d*) no surgical removal of the colon, one lung, ovary, or prostate; (*e*) not participating in another cancer screening or cancer prevention trial; (*f*) males not taking Proscar in the past 6 months, females not taking Novaldex in the past 6 months; (*g*) able to provide informed consent; (*h*) no more than one prostate-specific antigen test in the past 3 years (for subjects randomized after April 1995); and (*i*) no colonoscopy, sigmoidoscopy, or barium enema in the past 3 years (for subjects randomized after April 1995).

Subjects for this study were drawn from participants in the intervention arm of the trial at the University of Pittsburgh who underwent a screening flexible sigmoidoscopy. Nine hundred eighty-one subjects were invited by mail to participate in this ancillary study and 480 (48.9%) agreed. Participants were asked to undergo a single-slice CT scan through the L4-L5 interspace for quantification of VAT and, at a separate visit, a fasting blood draw and SQAT aspiration. The sample was enriched for subjects with a polyp on screening sigmoidoscopy (69.2%) compared with those with a negative exam (30.8%). Subjects were referred to personal physicians for evaluation of screen-detected abnormalities and were tracked to determine the results from subsequent diagnostic work-ups. Only subjects who underwent both CT scanning and a fasting blood draw were included in this analysis.

Measurement of IGF-1, IGFBP-3, and Insulin. IGF-1 was extracted using acid ethanol cryoprecipitation to remove residual IGFBPs from the serum[4] (28). Subsequently, the supernatant was assayed for IGF-1 using a polyclonal antibody to IGF-1 (Nichols Institute; San Juan Capistrano, CA). IGFBP-3 was analyzed by an immunoradiometric methodology (DSL, Webster, TX). All of the samples were assayed and extracted in duplicate. Each batch of 38 samples was analyzed simultaneously with 2 in-house control samples consisting of human IGF-1 serum. The interassay coefficient of variation was 6.6%. The molar ratio was calculated by multiplying 3.7 $\times$ IGF-1: IGFBP-3 (IGF-1:IGFBP-3). Fasting insulin was measured via a ^{125}I radioimmunoassay (Linco Research, Inc.), with a coefficient of variation of 2.6%.

Measurement of VAT. Subjects were scanned with a 9800-CT scanner (General Electric, Milwaukee, WI). The L4-L5 interspace was determined by review of the lateral scout film of the lower lumber spine. A single slice through the L4-L5 interspace, measuring 10 mm in size, was performed at 120 kVp and 170 mA with a scanning time of 2 s. Abdominal adipose tissue was calculated using commercially available CT software (GE Medical Systems, Milwaukee, WI). Adipose tissue area was determined electronically by setting the region of interest for attenuation values within the range of -190 to -30 Hounsfield units. Small alterations of the Hounsfield-unit range do not significantly alter VAT measurements (29–31). Using the trace function, the boundary separating subcutaneous and visceral fat was defined manually using a cursor, and the intra-abdominal adipose tissue area was recorded. Previous investigation has confirmed the reproducibility and repeatability of this technique (32, 33). Retroperitoneal adipose tissue was included in the VAT measurement. Total fat was determined by adding the sum of VAT and SQAT.

Statistical Methods. Mean values were compared with *t* tests. Spearman correlation coefficients were calculated for the comparison of insulin, IGF-1, IGFBP-3, and the molar ratio of IGF-1:IGFBP-3 with demographic, anthropometric, and fat-distribution measurements. Because of differences in fat distribution by gender, separate analyses for men and women were performed. A value of $P < 0.05$ was considered statistically significant. To detect nonlinear and dose-response relationships, we used gender-specific cutpoints to categorize subjects into quartiles according to BMI, body weight, VAT, SQAT, total abdominal fat, VAT as a percentage of total abdominal fat, and SQAT as a percentage of total abdominal fat. We then examined the distribution of hormone measures (IGF-1, IGFBP-3, IGF-1:IGFBP-3 molar ratio, and insulin) above and below gender-specific median cutpoints according to the quartile measures of obesity and body fat distribution. We used crude and Mantel-Haenszel age-adjusted odds ratios to measure the strengths of association between an elevated hormone measurement and obesity or body fat distribution quartile, the logit estimate of the odds ratio to calculate corresponding CIs, and the Cochran-Mantel-Haenszel correlation statistic to evaluate for linear trend (SAS version 8.01, SAS Institute, Inc., Cary, NC).

Results

Single-slice CT scans and blood studies were available for 432 community-based subjects (267 men, 165 women). Characteristics of the population sample are shown in Table 1. The mean age for men was 64.5 years $\pm$ 5.5 (range, 55–75) and for women, 63.5 $\pm$ 5.0 (range, 55–77; $P = 0.07$). There were no differences between men and women in BMI [weight (kg)/height (m^2); $P = 0.83$], but women weighed less (mean of 74.6 $\pm$ 14.1 kg compared with 88.6 $\pm$ 14.8 for men; $P < 0.0001$) and were shorter (mean of 1.63 $\pm$ 0.06 meters compared with 1.78 $\pm$ 0.07; $P < 0.0001$). Men had more VAT than women (201.5 $\pm$ 90.2 cm^3 *versus* 166.6 $\pm$ 76.9; $P < 0.0001$) but less SQAT (278.6 $\pm$ 108.6 cm^3 *versus* 390.0 $\pm$ 127.1; $P < 0.0001$). Men had a greater percentage of visceral fat and a lower percentage of subcutaneous fat as a percentage of total fat than women (Table 1). Overall, women had more total fat than men (556.7 $\pm$ 185.7 cm^3 *versus* 480.1 $\pm$ 173.7; $P < 0.0001$).

Men had higher mean IGF-1 levels than women [129.5 $\pm$ 45.8 ng/ml (range, 21–354) *versus* 108.9 $\pm$ 43.9 (range, 37–189); $P < 0.0001$] and lower IGFBP-3 levels [3048 $\pm$ 693 ng/ml (range, 1278–5653) *versus* 3430 $\pm$ 690 (range, 1169–5609); $P < 0.0001$]. The molar ratio of IGF-1:IGFBP-3 was significantly higher in men than women [0.156 $\pm$ 0.04 (range, 0.05–0.288) *versus* 0.116 $\pm$ 0.033 (range 0.047–0.200); $P < 0.0001$]. Fasting insulin levels were similar between men and women.

Spearman correlation coefficients describing associations between IGF measures (IGF-1, IGFBP-3, and IGF-1:IGFBP-3) and insulin with age, BMI, and fat distribution are shown for men and women in Tables 2A and 2B, respectively. In men and women, there was no significant relationship between IGF-1, IGFBP-3, and the ratio IGF-1:IGFBP-3 with total fat, BMI, or

[4] Internet address: http://members.mint.net/ea6bii/rogue/Methods.html.

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Table 1 Characteristics of the study subjects

	Men (n = 267) mean (±SD)	Women (n = 165) mean (±SD)	P
Demographics			
Age (yr)	64.5 (±5.5)	63.5 (±5.0)	0.07
Anthropometrics			
BMI (kg/m^2)	28.1 (±4.4)	28.0 (±5.1)[a]	0.83
Height (m)	1.78 (±0.07)	1.63 (±0.06)	<0.0001
Weight (kg)	88.6 (±14.8)	74.6 (±14.1)[a]	<0.0001
VAT (cm^3)	201.5 (±90.2)	166.6 (±76.9)	<0.0001
Visceral fat percentage (% of total) (VAT %)	41.6 (±9.4)	29.4 (±7.3)	<0.0001
SQAT (cm^3)	278.6 (±108.6)	390.0 (±127.1)	<0.0001
Subcutaneous fat percentage (% of total) (SQAT %)	58.4 (±9.4)	70.6 (±7.3)	<0.0001
Total fat (cm^3)	480.1 (±173.7)	556.7 (±185.7)	<0.0001
IGF and IGFBP			
IGF-1 (ng/ml)	129.5 (±45.8)	108.9 (±43.9)	<0.0001
IGFBP-3 (ng/ml)	3048 (±693)	3430 (±690)	<0.0001
Ratio (molar)	0.156 (±0.040)	0.116 (±0.033)	<0.0001
Insulin (μU/ml)	19.0 (±16.4)	18.6 (±17.8)	0.84

[a] n = 164 (because of missing weight).

Table 2 Spearman correlation coefficients

	IGF-1	IGFBP-3	Molar ratio	Insulin
A. Spearman correlation coefficients for men (n = 267)				
Age	−0.22 (P = 0.000)	−0.17 (P = 0.005)	−0.16 (P = 0.009)	−0.02 (P = 0.72)
BMI	−0.02 (P = 0.691)	0.03 (P = 0.664)	0.01 (P = 0.843)	0.49 (P = 0.0001)
Weight	−0.02 (P = 0.783)	0.04 (P = 0.500)	0.00 (P = 0.936)	0.48 (P = 0.0001)
VAT	−0.01 (P = 0.896)	0.04 (P = 0.529)	0.00 (P = 0.944)	0.49 (P = 0.00001)
VAT %	0.01 (P = 0.880)	0.01 (P = 0.874)	0.00 (P = 0.969)	0.13 (P = 0.04)
SQAT	−0.03 (P = 0.627)	0.03 (P = 0.652)	0.00 (P = 0.956)	0.43 (P = 0.0001)
SQAT %	−0.01 (P = 0.880)	−0.01 (P = 0.874)	0.00 (P = 0.969)	−0.13 (P = 0.04)
Total fat	−0.02 (P = 0.749)	0.05 (P = 0.419)	0.00 (P = 0.959)	0.53 (P = 0.0001)
Insulin	−0.08 (P = 0.22)	−0.03 (P = 0.59)	−0.03 (P = 0.62)	
B. Spearman correlation coefficients for women (n = 165)				
Age	−0.02 (P = 0.843)	−0.14 (P = 0.067)	0.05 (P = 0.565)	0.12 (P = 0.12)
BMI	0.00 (P = 0.961)[a]	0.07 (P = 0.373)[a]	−0.02 (P = 0.798)[a]	0.64 (P = 0.0001)
Weight	−0.03 (P = 0.658)[a]	0.09 (P = 0.258)[a]	−0.07 (P = 0.362)[a]	0.58 (P = 0.0001)
VAT	−0.05 (P = 0.513)	0.01 (P = 0.873)	−0.05 (P = 0.555)	0.60 (P = 0.0001)
VAT %	−0.08 (P = 0.320)	−0.09 (P = 0.276)	−0.03 (P = 0.726)	0.29 (P = 0.0002)
SQAT	0.00 (P = 0.954)	0.12 (P = 0.121)	−0.07 (P = 0.388)	0.59 (P = 0.0001)
SQAT %	0.08 (P = 0.320)	0.09 (P = 0.276)	0.03 (P = 0.726)	−0.29 (P = 0.0002)
Total fat	−0.03 (P = 0.719)	0.09 (P = 0.275)	−0.07 (P = 0.367)	0.65 (P = 0.0001)
Insulin	0.10 (P = 0.18)	0.11 (P = 0.14)	0.07 (P = 0.38)	

[a] n = 164.

visceral or subcutaneous fat. In men, there was a statistically significant negative correlation between IGF-1 and age (r, −0.22; P = 0.0001), IGFBP-3 and age (r, −0.17; P = 0.005), and the molar ratio of IGF-1:IGFBP-3 and age (r, −0.016; P = 0.009), although the absolute values of the correlation coefficients were small. In women, there was no statistically significant age association with IGF-1 or the molar ratio, and a borderline association with IGFBP-3 (r, −0.014; P = 0.07). Adjusting for age in a multivariate model did not affect the results.

In contrast, fasting insulin was highly associated with anthropometric and quantitative measures of obesity in men and women. For example, fasting insulin was highly associated with VAT in men (r, 0.49; P = 0.0001) and women (r, 0.60; P = 0.0001).

Table 3 shows the crude and age-adjusted odds ratio of an IGF-1, IGFBP-3, IGF-1:IGFBP-3 ratio, or insulin measurement above the median for men and women in quartiles 2, 3, and 4 of VAT relative to persons in quartile 1. Insulin showed a strong, consistent dose-response relationship with VAT quartile. The age-adjusted odds of having an insulin measurement above the median was 48.9-fold (95% CI, 14.4–166.0; P < 0.0001) greater in men in quartile 4 of VAT, relative to men in quartile 1. The corresponding odds ratio in women was 30.7 (95% CI, 7.9–118.8; P < 0.0001; Table 3). In contrast, the odds of having an IGF-1, IGFBP-3, or IGF-1:IGFBP-3 above the median was similar in men and women regardless of their quartile of VAT. Similar evaluation did not produce evidence for a linear association between any IGF-related measure and quartile levels of any of the other measures of obesity including BMI, weight, subcutaneous fat, total abdominal fat, VAT as a percentage of total abdominal fat, and SQAT as a percentage of total abdominal fat (data not shown).

Because we intentionally over-sampled persons with abnormal flexible sigmoidoscopy results, we used ANOVA to examine the effects of obesity and body fat distribution on

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Table 3 Relationship between VAT and insulin and the IGF-1 axis

	Q1[a]	Q2	Q3	Q4	Trend test *P*
Men					
VAT (cm^3)	<135.8	135.8–187.5	187.6–254.4	>254.4	
IGF-1 (>127)	36	30	34	35	
IGF-1 (≤127)	30	37	33	32	
OR unadj (95% CI)	1.00	0.68 (0.34–1.34)	0.86 (0.43–1.70)	0.91 (0.46–1.80)	0.977
OR age-adj (95% CI)	1.00	0.79 (0.38–1.65)	1.07 (0.51–2.26)	1.06 (0.52–2.16)	0.595
IGFBP-3 (>3066.5)	33	29	33	39	
IGFBP-3 (≤3066.5)	33	38	34	28	
OR unadj (95% CI)	1.00	0.76 (0.39–1.51)	0.97 (0.49–1.92)	1.39 (0.70–2.76)	0.262
OR age-adj (95% CI)	1.00	0.83 (0.41–1.68)	1.15 (0.54–2.44)	1.11 (0.53–2.33)	0.157
Ratio (>0.15753)	33	32	30	39	
Ratio (≤0.15753)	33	35	37	28	
OR unadj (95% CI)	1.00	0.91 (0.46–1.80)	0.81 (0.41–1.60)	1.39 (0.70–2.76)	0.428
OR age-adj (95% CI)	1.00	0.91 (0.44–1.88)	0.92 (0.44–1.95)	1.95 (0.88–4.30)	0.210
Insulin (>14.6)	13	27	36	58	
Insulin (≤14.6)	53	40	31	9	
OR unadj (95% CI)	1.00	2.75 (1.26–6.00)	4.73 (2.18–10.3)	26.3 (10.4–66.5)	<0.0001
OR age-adj (95% CI)	1.00	2.88 (1.23–6.73)	5.87 (2.44–14.1)	48.9 (14.4–166.0)	<0.0001
Women					
VAT (cm^3)	<109.4	109.4–155.3	155.4–206.1	>206.1	
IGF-1 (>104)	18	28	19	21	
IGF-1 (≤104)	23	13	22	21	
OR unadj (95% CI)	1.00	2.75 (1.12–6.78)	1.10 (0.46–2.64)	1.28 (0.54–3.03)	0.914
OR age-adj (95% CI)	1.00	2.82 (1.08–7.34)	1.00 (0.38–2.60)	1.30 (0.52–3.23)	0.865
IGFBP-3 (>3378.0)	18	20	26	19	
IGFBP-3 (≤3378.0)	23	21	15	23	
OR unadj (95% CI)	1.00	1.22 (0.51–2.90)	2.22 (0.91–5.37)	1.06 (0.44–2.51)	0.604
OR age-adj (95% CI)	1.00	1.27 (0.51–3.16)	2.21 (0.84–5.79)	1.21 (0.48–3.02)	0.506
Ratio (>0.11807)	17	23	18	24	
Ratio (≤0.11807)	24	18	23	18	
OR unadj (95% CI)	1.00	1.80 (0.75–4.33)	1.10 (0.46–2.65)	1.88 (0.79–4.50)	0.315
OR age-adj (95% CI)	1.00	1.90 (0.75–4.83)	1.30 (0.46–3.72)	1.92 (0.76–4.88)	0.319
Insulin (>13.7)	7	17	24	35	
Insulin (≤13.7)	34	24	17	7	
OR unadj (95% CI)	1.00	3.44 (1.24–9.58)	6.86 (2.46–19.1)	24.3 (7.70–76.6)	<0.0001
OR age-adj (95% CI)	1.00	2.01 (0.64–6.38)	3.96 (1.36–11.6)	30.7 (7.92–118.8)	<0.0001

[a] Q, quartile; OR, odds ratio; unadj, unadjusted; age-adj, adjusted for age.

mean levels of IGF-1, IGFBP-3, IGF-1:IGFBP-3, and insulin, while adjusting for the effects of disease state. From completed diagnostic evaluations, we could unambiguously classify 409 (94.7%) of 432 subjects into one of three categories (183 with proximal and/or distal colorectal adenoma at diagnostic colonoscopy or sigmoidoscopy, 88 without adenoma at diagnostic colonoscopy, and 138 without polyp at the initial screening sigmoidoscopy). Separate ANOVA models, with terms for gender, age, age-gender interaction, disease state, and gender-disease interaction, did not uncover any consistent or significant association between any measure of obesity and any measure of the IGF-1 axis (data not shown). However, associations between adipose tissue measurements and insulin were strong and consistent.

Discussion

Insulin, IGF-1, IGFBP-3, and the ratio of IGF-1:IGFBP-3 have been associated with cancer. Understanding the determinants of IGF-1 is important because it may allow the identification of factors that affect the relationship between IGF-1 and disease. It may also allow identification of modifiable factors, which could be used to attenuate the risk induced by high-circulating free IGF-1.

In this investigation, IGF-1, IGFBP-3, insulin, and adipose tissue distribution measured by CT scanning were examined in a large, asymptomatic, community-based sample. CT scanning is a highly accurate, reproducible, and repeatable measure of visceral fat (29, 32, 33). A single-slice CT scan through the L4-L5 interspace is highly correlated with VAT measurement assessed by complete abdominal scanning and is more accurate than anthropometric assessment of VAT (32). For example, sagittal diameter is equivalent to waist circumference in estimating VAT (34), but as small as a 2-cm range in sagittal diameter can be associated with a 3-fold difference in VAT (32). Using this accurate technique, we found no significant linear or nonlinear relationship between obesity, estimated by BMI or weight or by total, visceral, or subcutaneous fat measured by abdominal CT scan, and the IGF-1 axis. Nor did the relative percentage of SQAT or VAT correlate with the IGF-1 axis.

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In contrast, and consistent with previous investigations (23–25), insulin was highly correlated with obesity and with VAT and demonstrated a strong, consistent, dose-response relationship to VAT quartile. The age-adjusted odds of having an insulin measurement above the median was nearly 50-fold greater in men in quartile 4 relative to men in quartile 1, and the corresponding odds ratio in women was over 30-fold greater.

Postulating a relationship between obesity and IGF-1 is reasonable, because obesity can affect growth hormone secretion, which is the primary determinant of IGF-1 production in the liver (10). Nutritional status and growth affect the IGF axis (35), and significant perturbations such as protein-calorie malnutrition or fasting can affect IGF-1 levels (1).

The relationship between IGF-1 and obesity has varied in previous investigations. In a sample of 351 subjects from the Baltimore Longitudinal Aging Study, IGF-1 was not significantly related to BMI or waist:hip ratio after controlling for age (11). Similar results were seen in a Swedish cohort study (36). Alternatively, Copeland *et al.* (37) found a negative association (r, -0.25; $P = 0.05$) between IGF-1 and BMI in a sample of 62 men, but no association between IGF-1 and BMI in a sample of 45 women, whereas Nystrom *et al.* (38) found an association between BMI and IGF-1 in women and not in men. Only one small study of 27 obese men (BMI >25) has used CT scanning to quantify adipose tissue distribution in relation to IGF-1 (39). A strong negative association between IGF-1 and VAT was noted (r, -0.40), but no association was seen with total fat. An accurate estimation of VAT is important, because our previous research has shown that using anthropometric variables such as BMI or sagittal diameter, can lead to an inaccurate estimation of VAT (32). For example, individuals with identical measurements of BMI may have a VAT level that varies by 3-fold (32). The size of this study and the technique used to measure adipose tissue distribution make this study the most definitive in examining a relationship between obesity and the IGF-1 axis. Additional strengths include the fact that subjects are community-based, healthy volunteers in a cancer-screening trial.

Several studies have demonstrated a decline in IGF-1 with aging (11, 36–38, 40). It is hypothesized that a decline in IGF-1 with aging corresponds to the decrease in growth hormone that occurs with aging. This decrease is hypothesized to contribute to the reduction in lean body mass and the relative increase in adipose tissue, and particularly VAT, that occurs with aging. In this investigation, we did not observe an association between IGF-1 and aging in women, but we did observe a relatively weak inverse relationship between IGF-1 and IGFBP-3 and age in men. Several factors may explain our findings. The studies that show a decline in IGF-1 with aging include a wide age range, usually from age 20 to 80 years of age or more (11, 36, 37, 40). The decline in IGF-1 during middle age is small (11, 36) or minimal (41). Thus, IGF-1 levels decrease when younger subjects are evaluated in comparison with older subjects, but within a narrow age range of 55–74 years, such as in this study, a strong relationship between age and IGF-1 level may not be observed.

In this investigation, in agreement with other studies (29, 30), men had a higher amount of VAT than women. Men also had an increased amount of IGF-1 in comparison with women of a similar age. This finding is in agreement with the results obtained in a Swedish cohort study (36). The physiological implications and etiology of a higher IGF-1 in men than in women merits further exploration, but our results indicate that VAT is not the likely explanation.

Although insulin and IGFs are often lumped together when discussing a possible causal relationship to cancer, this study suggests that the determinants of insulin and IGFs differ. Thus, whereas considerable data show that insulin levels are strongly influenced by VAT, including a highly significant relationship between insulin and VAT in this study, this study suggests that VAT is not a determinant of IGF-1. The biological relationship between insulin and IGFs is complex. Insulin can affect the bioactivity of IGF-1 by a variety of possible mechanisms including altering growth hormone receptor levels in the liver (42) and by affecting hepatic IGFBP-1 and IGFBP-2 production (43). In this sample, insulin was not associated with IGF-1 or IGFBP-3 in men or women, a relationship consistent with that found in men participating in a cohort study of prostate cancer (44). However, one study in women did show an association between C-peptide and IGF-1 and IGFBP-3 (3).

A divergence between insulin and IGFs in relation to disease is consistent with recent results in colorectal cancer. The relationship between visceral obesity, insulin, and incident colorectal cancer has been demonstrated in a prospective study (19). A recent prospective cohort study confirmed the relationship between insulin and colorectal cancer but failed to demonstrate any association between IGF-1 and colorectal cancer (3).

Several limitations should be acknowledged. The subjects were drawn from a community-based cancer-screening trial, in which more educated, more affluent, nonminority participants are overrepresented (45). These results may not be applicable to specific minority or ethnic groups. Similarly, participants were healthy volunteers, but relationships between VAT and the IGF axis in disease require additional study. Subjects with abnormalities on screening sigmoidoscopy are overrepresented in this sample. However, it should be noted that these polyps were detected by screening, not by symptoms, and would not have been detected otherwise. Also, our analysis shows that the lack of association between adipose tissue distribution and the IGF axis was unchanged after accounting for the presence of neoplastic polyps. Thus, regardless of the relationship between the IGF axis or adipose tissue distribution and colonic polyps, our data do not support an association between adipose tissue distribution and the IGF-1 axis.

In conclusion, obesity and adipose tissue distribution do not correlate with IGF-1, IGFBP-3, or the molar ratio of the two. The study of VAT, insulin, and neoplastic disease is difficult because as disease develops, weight and VAT can change. Thus, prospective cohort studies, which can examine the relationship of obesity and adipose tissue distribution before the onset of disease, are preferable. Further exploration of the relationship between the IGF-1 axis, adipose tissue distribution, and neoplastic disease is needed. Our data do not diminish the association of the IGF-1 axis with cancer, but the lack of association between obesity and the IGF-1 axis suggests that the IGF-1 axis is not a likely mediator between VAT and disease.

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