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Body mass index, waist circumference and waist–hip ratio and serum levels of IGF-I and IGFBP-3 in European women

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Abstract

Objective:

To examine the relationship between body mass index (BMI) and waist–hip ratio (WHR) with serum levels of insulin-like growth factor-I (IGF-I), and its binding protein (IGFBP)-3.

Design:

Cross-sectional study on 2139 women participating in a case–control study on breast cancer and endogenous hormones. Data on lifestyle and reproductive factors were collected by means of questionnaires. Body height, weight, waist and hip circumferences were measured. Serum levels of IGF-I and insulin-like binding protein (IGFBP)-3 were measured by enzyme-linked immunosorbent assays. Adjusted mean levels of IGF-I and IGFBP-3 across quintiles of BMI, waist circumference, and WHR were calculated by linear regression. Results were adjusted for potential confounders associated with IGF-I and IGFBP-3.

Results:

Adjusted mean serum IGF-I values were lower in women with BMI<22.5 kg/m^2 or BMI>29.2 kg/m^2 compared to women with BMI within this range ($P_{heterogeneity}<0.0001$, $P_{trend}=0.35$). Insulin-like growth factor-I was not related to WHR after adjustment for BMI. IGF-binding protein-3 was linearly positively related to waist and WHR after mutual adjustment. The molar ratio IGF-I/IGFBP-3 had a non-linear relation with BMI and a linear inverse relationship with WHR ($P_{trend}=0.005$).

Conclusions:

Our data confirm the nonlinear relationship of circulating IGF-I to total adiposity in women. Serum IGFBP-3 was positively related to central adiposity. These suggest that bioavailable IGF-I levels could be lower in obese compared to non-obese women and inversely related to central adiposity.

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Introduction

Elevated serum levels of insulin-like growth factor-I (IGF-I), measured as absolute concentrations or expressed relative to levels of its major plasmatic-binding protein, IGFBP-3, have been associated with increased risk of several common cancers such as breast, colorectal, prostate and lung.[1, 2] On the other hand, higher plasma concentrations of IGF-I have been found to be associated with a reduced risk of osteoporosis,[3] diabetes[4] and possibly heart disease.[5]

Insulin-like growth factor-I, together with insulin, is central to the regulation of anabolic (growth) processes as a function of available energy and essential nutrients (e.g. amino acids) from body reserves and diet.[6] In blood circulation, over 75% of IGF-I is bound to the insulin-like binding protein (IGFBP)-3.[7] Circulating IGF-I levels are largely determined by genetic factors and age,[8, 9] and are also affected by sex, anthropometric indices, physical activity, exogenous sex hormones, smoking, alcohol consumption[10] and nutritional status.[6] Circulating levels of IGF-I and IGFBP-3 concentrations vary considerably between normal individuals, but blood levels in each individual are relatively constant. Energy and/or protein deprivation markedly lower IGF-I.[11, 12] Excess energy intake may increase IGF-I but this does not appear to affect IGF-I levels as strongly as nutritional restriction.[6]

The relation of IGF-I and IGFBP-3 with body weight and body fat distribution is not well understood. Circulating IGF-I levels in obese subjects would be expected to be low, because growth hormone (GH) stimulates the liver to produce IGF-I and because there is an inverse relationship between obesity and GH secretion. However, findings of studies on obese subjects are conflicting, with serum concentrations of total IGF-I reported to be relatively low,[13, 14, 15, 16] unchanged[17, 18] or increased.[19, 20] Several cross-sectional studies of adiposity and circulating IGF-I have found no relationship[21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32] while a nonlinear relationship of body mass index (BMI) with IGF-I has been observed in some large studies.[33, 34, 35, 36] The data on the relationship between IGFBP-3, the main binding protein of IGF-1, and obesity are not consistent.[27, 29, 30, 31, 32, 34, 36, 37]

Given the potential role of IGF-I in the development of several chronic diseases, it is of interest to investigate whether increased body weight, a modifiable risk factor, is related to circulating levels of IGF-I. Excess body weight is a risk factor for the development of major chronic diseases, including some cancers,[38] and mortality.[39, 40] Some evidence indicates that leanness may be associated with an increase in mortality.[39]

Here we present the cross-sectional relationship of BMI, waist circumference and waist–hip ratio (WHR) with serum levels of IGF-I and IGFBP-3 in a large sample of 2139 free-living women from eight European countries. We especially wanted to examine whether the nonlinear relationship between BMI and IGF-I levels could be supported in these data.

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Materials and methods

Study population

The study is comprised of a sample of women participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) – a large, multicentre cohort of about 370 000 women and 150 000 men, recruited between 1992 and 1998 in 10 western European countries. A detailed description of EPIC can be found elsewhere.[41, 42] In the EPIC study, data were collected on weight, height, waist and hip circumferences, diet over the 12 months before enrolment, alcohol use, smoking status, physical activity, menstrual and reproductive history, current and past use of oral contraceptives and previous illnesses. Blood samples were collected according to a standardized protocol. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and all local institutes where subjects were recruited for the EPIC study. All participants had given written consent for future analysis of their blood samples.

The women in the present study were selected from 2278 control subjects of a nested case–control study on the relationship between endogenous hormones and breast cancer.[43] The women included were from 19 recruitment centres in eight countries: Denmark, the Netherlands, the United Kingdom (UK), France, Germany, Spain, Italy and Greece. Only women who were free of cancer and did not use oral contraceptives or any hormone replacement therapy at time of blood donation were included in the study. We excluded 14 women taking insulin as medication for diabetic conditions and women who had self-reported or missing anthropometric data, leaving 2139 women for the present analysis.

Anthropometric measurements

The women had their body height, waist and hip circumferences measured to the nearest 0.5 cm and weight to the nearest 0.1 kg, with subjects wearing no shoes. Body mass index was calculated as weight divided by height (kg/m^2). Waist circumference was measured either at the narrowest torso circumference (France, Italy, the United Kingdom, Utrecht, The Netherlands) or at the midpoint between the lower ribs and iliac crest (Bilthoven, the Netherlands, Potsdam, Germany, Malmo, Sweden). In Spain, Greece, Denmark and Heidelberg (Germany), a combination of methods was used, although the majority of participants were measured at the narrowest circumference. Hip circumference was measured at the widest circumference (France, Italy, Spain, Bilthoven, the Netherlands, Greece, Malmo, Sweden) or over the buttocks (UK, Utrecht, The Netherlands, Germany, Denmark). The waist and hip circumferences measurements were used to construct a WHR.

Laboratory assays

Fasting and non-fasting blood samples were collected according to a standardized protocol. From each subject, 30 ml of blood was drawn using 10 ml Safety Monovettes (Sartstedt, Nümbrecht, Germany). Filled syringes were kept at 5–10°C, protected from light, and transferred to a local laboratory for further processing and aliquoting. One dry syringe was used to prepare serum. After centrifugation (1550 g for 20 min), blood fractions (serum, plasma, red cells, buffy coat) were aliquoted in 28 plastic straws of 0.5 ml each (12 plasma, eight serum, four erythrocytes and four buffy coat for DNA), which were heat sealed at the ends and stored in liquid nitrogen (-196°C). The protocol differed slightly for

Denmark. We analysed samples from women who belonged to different EPIC centres or different menopausal subgroups in a total of 49 separate batches.

We performed all hormone assays on never thawed serum aliquots in the laboratory of the Nutrition and Hormones Group at IARC. We measured serum levels of IGF-I and IGFBP-3 by enzyme-linked immunosorbent assays from Diagnostic System Laboratories (DSL, Webster, TX, USA). Insulin-like growth factor-I assays included an acid-ethanol precipitation step to eliminate IGF-I-binding proteins to avoid their interference with the IGF-I measurement. The mean intra- and inter-batch coefficients of variation for IGF-I were 6.2 and 16.2%, respectively. The corresponding figures for IGFBP-3 were 7.2 and 9.7%.

Statistical analyses

We estimated least-square means of IGF-I and IGFBP-3 and the IGF-I/IGFBP-3 molar ratio by quintiles and deciles of BMI, waist and hip circumferences, and WHR defined over the entire study population. The hormone measurements were transformed via the natural log to best approximate normal distribution. These values have been transformed back to normal physiological levels in the tables for the purpose of presentation. Analysis of variance and covariance were used to test for differences in crude and adjusted mean levels of IGF-I, IGFBP-3 and molar ratio IGF-I–IGFBP-3. P-values for linear trend were estimated by modelling hormone measurements using the median value in each quintile. Each of the following factors was evaluated as a potential confounder of the relation between the anthropometric measures and serum IGF-I levels: age at enrolment in 5-year intervals (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65+), age at menarche (<12, 12, 13, 14, 15, 16+), number of children (0, 1, 2, 3, 4, 5+), use of oral contraceptives (former/never), use of hormone replacement therapy (former/never), smoking status (never smoker, current smoker, former smoker), physical activity (low, moderately inactive, moderately active, active) and alcohol consumption in g/day (non-consumers, quintiles of intake in consumers), based on previous studies and on the observed association with the anthropometric variables and the hormone measurements. Only age and laboratory batch were kept in the final models, because inclusion of the above-listed potential confounding variables in the models did not change the results materially. Indicator terms for laboratory batch were included in all the models. In some analysis, BMI and WHR were mutually adjusted.

The analyses were conducted using SAS Statistical Software, version 8 (SAS Institute, Cary, NC, USA), and all statistical tests were two sided. For all analyses, P-values <0.05 were considered statistically significant.

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Results

Selected characteristics of the study population are shown in Table 1. The women in the cross-sectional study were aged 32–77 years. Mean age at study entry was 55 years. Mean age at menopause was 49 years, and 37.9% of the women were premenopausal. The overall crude serum levels for IGF-I was 31.2 nmol/l and for IGFBP-3, 126.1 nmol/l. The Pearson's partial correlation coefficient between serum levels of IGF-I and IGFBP-3 was 0.45 after adjustment for age and batch ($P<0.0001$).

Table 1 - Selected characteristics of 2139 women participating in the EPIC.

Characteristics	Mean (s.d.)
Age at entry (years)	54.6 (8.6)
IGF-I (nmol/l)	31.2 (10.1)
IGFBP-3 (nmol/l)	125.9 (45.4)
Molar ratio IGF-I/IGFBP-3	0.276 (0.141)
Body height (cm)	160.4 (6.8)
Body weight (kg)	67.6 (11.7)
Body mass index (kg/m^2)	26.3 (4.6)
Waist (cm)	82.8 (11.1)
Hip (cm)	103.2 (9.3)
Waist–hip ratio	0.80 (0.06)
Age at menarche (years)	13.1 (1.6)
Age at menopause (years)	49.0 (4.8)
Alcohol intake (g/day)	7.5 (11.2)
	Percentage of women (%)
Parous	87.1
Previous OC use	45.7
Previous HRT use	14.2
Ex-smokers	24.1
Current smokers	16.7

EPIC, European Prospective Investigation into Cancer and Nutrition; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like binding protein (IGFBP)-3.

IGF-I and –IGFBP-3 were transformed using the logarithm. Values in the tables are back transformed to physiological values. Values are means (s.d.) for continuous variables and percentage of women with the characteristics for categorical variables.

OC: Oral Contraception.

HRT: Hormone Replacement Therapy.

The relationship of serum IGF-I and IGFBP-3 with potential confounders is shown in Table 2. Mean IGF-I values were inversely related to age ($P_{trend}<0.0001$) but not significantly related to age at menarche ($P_{trend}=0.07$). Mean values of serum IGFBP-3 tended to be lower in older women, but the relationship was not statistically significant. Means of serum IGF-I were inversely related to age at menarche ($P_{trend}=0.007$). Insulin-like growth factor-I and IGFBP-3 were not related to parity, previous use of oral contraceptives or hormone replacement therapy, or smoking status. Alcohol intake was inversely related to serum IGF-I ($P_{trend}=0.03$) and positively related to IGFBP-3 ($P_{trend}=0.02$).

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Table 2 - Adjusted mean levels of IGF-I and IGFBP-3 by age, reproductive and lifestyle variables in 2139 European women.

Variables	IGF1 (nmol/l)	IGFBP3 (nmol/l)
Age (years)		
<40	38.7	123.3
40–44	32.9	117.3
45–49	30.6	117.6
50–54	29.6	119.2
55–59	28.3	116.9
60–64	27.1	118.3
65+	24.8	113.7
$P_{heterogeneity}/P_{trend}$	<0.0001/<0.0001	0.34/0.17
Age at menarche (years)		
<12	30.6	121.3
12	30.3	120.5
13	29.7	116.6
14	29.8	117.9
15	29.1	116.6
16+	29.8	115.4
$P_{heterogeneity}/P_{trend}$	0.41/0.07	0.06/0.007
Parity (number of children)		
0	29.3	115.0
1	30.1	117.8
2	30.6	119.8
3	29.4	115.0
4	29.3	119.0
5+	28.8	116.1
$P_{heterogeneity}/P_{trend}$	0.12/0.41	0.03/0.77
Oral contraceptive use		
Never	29.9	117.1
Former	30.2	118.1
$P_{heterogeneity}$	0.61	0.46
Hormone replacement therapy use		
Never	30.2	121.3
Former	30.5	119.2
$P_{heterogeneity}$	0.57	0.29
Smoking status		
Never	31.1	118.9
Former	31.3	118.5
Current	30.3	119.2
$P_{heterogeneity}/P_{trend}$	0.30/0.30	0.93/0.92
Alcohol intake (g/day)		
0	31.1	117.1
<0.84	30.7	118.1
0.84–3.30	31.1	116.9
3.30–8.13	31.4	119.0
8.13–15.39	30.9	120.3
>15.39	29.2	121.4
$P_{heterogeneity}/P_{trend}$	0.03/0.03	0.23/0.02

IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like binding protein (IGFBP)-3.

IGF-I and IGFBP-3 values are least-square means adjusted for laboratory batch, body mass index in quintiles and all other factors in the table. Analyses of variance and covariance were used to test for differences in mean levels of IGF-I and IGFBP-3. *P*-values for linear trend were estimated by modelling hormone measurements using the median value in each category.

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Mean serum IGF-I showed a significant but nonlinear inverse association with BMI ($P_{heterogeneity}<0.0001$, $P_{trend}=0.35$) (Table 3). Mean serum IGF-I values were 28.9 nmol/l in women with BMI lower than 22.5 kg/m^2 and 28.0 nmol/l in women with BMI higher than 29.7 kg/m^2 (mostly obese women[44]), respectively. These values were lower than the mean IGF-I values observed in women with BMI within that range (normal weight and overweight women). The nonlinear relationship of BMI with serum IGF-I remained after adjustment for WHR. There was a significant nonlinear relationship between serum IGF-I and waist circumferences ($P_{heterogeneity}=0.01$, $P_{trend}=0.16$) in models adjusted for age, and laboratory batch (Table 3). Mean values of serum IGF-I tended to increase from the 1st up to the 3rd quintile of waist circumference, but in women in the 4th and 5th quintile (more than 84 cm of waist circumference), the relationship with serum IGF-I was inversed. Serum IGF-I was not significantly related to WHR.

Table 3 - Adjusted means (95% confidence interval) of serum IGF-I, IGFBP-3 and ratio IGF-I/IGFBP-3 by quintiles of anthropometric measurements in 2139 European women.

Anthropometric variable	***IGF-I (nmol/l)***	***IGFBP-3 (nmol/l)***	***Ratio IGF-I/IGFBP-3***
BMI (kg/m ^{2})[a]			
<22.5	28.9 (28.1–29.8)	116.5 (113.9–119.1)	0.246 (0.239–0.252)
22.5–24.6	29.8 (28.9–30.6)	117.1 (114.6–119.8)	0.252 (0.245–0.259)
24.6–26.6	30.7 (29.9–31.6)	121.4 (118.7–124.1)	0.250 (0.243–0.257)
26.6–29.7	30.3 (29.5–31.2)	121.3 (118.6–124.0)	0.249 (0.243–0.256)
>29.7	28.0 (27.2–28.9)	122.1 (119.4–124.9)	0.227 (0.220–0.233)
$P_{heterogeneity}/P_{trend}$	<0.0001/0.35	0.01/0.001	<0.0001/0.0003
BMI (kg/m ^{2})[b]			
<22.5	29.0 (28.1–29.8)	118.3 (115.6–121.1)	0.242 (0.235–0.249)
22.5–24.6	29.8 (28.9–30.6)	118.0 (115.4–120.7)	0.250 (0.243–0.257)
24.6–26.6	30.7 (29.9–31.6)	121.6 (118.9–124.3)	0.249 (0.243–0.256)
26.6–29.7	30.3 (29.5–31.2)	120.3 (117.7–123.0)	0.251 (0.244–0.258)
>29.7	28.0 (27.2–28.9)	119.7 (116.8–122.6)	0.231 (0.224–0.240)
$P_{heterogeneity}/P_{trend}$	<0.0001/0.42	0.34/0.28	<0.0001/0.12
WHR[a]			
<0.75	29.3 (28.4–30.1)	113.9 (111.4–116.5)	0.254 (0.247–0.261)
0.75–0.78	29.5 (28.7–30.4)	117.7 (115.2–120.3)	0.249 (0.243–0.256)
0.78–0.81	29.9 (29.1–30.8)	119.2 (116.6–121.8)	0.248 (0.241–0.254)
0.81–0.85	30.0 (29.2–30.9)	122.4 (119.7–125.2)	0.243 (0.236–0.250)
>0.85	29.0 (28.1–29.8)	125.0 (122.2–127.9)	0.229 (0.223–0.236)
$P_{heterogeneity}/P_{trend}$	0.37/0.82	<0.0001/<0.0001	<0.0001/<0.0001
WHR[b]			
<0.75	28.9 (28.0–29.8)	114.3 (111.6–117.0)	0.250 (0.243–0.258)
0.75–0.78	29.3 (28.5–30.2)	117.9 (115.3–120.6)	0.247 (0.240–0.254)
0.78–0.81	29.9 (29.0–30.7)	119.2 (116.7–121.9)	0.247 (0.241–0.254)
0.81–0.85	30.2 (29.4–31.1)	122.2 (119.5–125.0)	0.245 (0.238–0.252)
>0.85	29.4 (28.5–30.3)	124.6 (121.7–127.6)	0.234 (0.227–0.240)
$P_{heterogeneity}/P_{trend}$	0.26/0.27	<0.0001/<0.0001	0.02/0.005
Waist (cm)			
<73	28.9 (28.0–29.8)	114.6 (111.9–117.4)	0.249 (0.242–0.257)
73–79	30.3 (29.4–31.1)	117.8 (115.3–120.3)	0.255 (0.248–0.262)
79–84	30.2 (29.3–31.1)	121.3 (118.6–124.1)	0.248 (0.241–0.255)
84–92	29.9 (29.1–30.8)	120.2 (117.7–122.8)	0.245 (0.239–0.252)
>92	28.5 (27.6–29.3)	124.2 (121.5–127.1)	0.226 (0.220–0.233)
$P_{heterogeneity}/P_{trend}$	0.01/0.16	<0.0001/<0.0001	<0.0001/<0.0001
Hip (cm)			
<96	29.2 (28.4–30.1)	119.4 (116.8–122.2)	0.242 (0.236–0.249)
96–100	29.9 (29.0–30.8)	118.2 (115.5–121.0)	0.251 (0.244–0.258)
100–104	30.1 (29.2–31.0)	118.6 (116.0–121.3)	0.251 (0.244–0.258)
104–110	30.1 (29.3–31.0)	120.2 (117.7–122.8)	0.246 (0.240–0.253)
>110	28.5 (27.7–29.3)	121.4 (118.7–124.1)	0.233 (0.227–0.239)
$P_{heterogeneity}/P_{trend}$	0.04/0.15	0.51/0.16	0.001/0.01

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IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like binding protein (IGFBP)-3.

IGF-I and IGFBP-3 values are adjusted least-square means (95% confidence interval). Analysis of variance was used to test for differences in mean levels of IGF-I and IGFBP-3. *P*-values for linear trend were estimated by modelling hormone measurements using the median value in each quintile.

[a] Results are adjusted for age, and laboratory batch.

[b] Results are additionally adjusted for BMI or WHR.

In order to examine the nonlinear relationship of the mean serum IGF-I levels with BMI, we first categorized the study population by deciles of BMI (Figure 1a) and estimated the least-square means of IGF-I in each category. We then classified the study population into two groups using the BMI of 26 kg/m^2 as cutpoint. This value was selected after looking at the distribution by deciles of BMI. We then conducted linear regression analyses of BMI on log-transformed peptide values for the two groups separately. The inverse relationship between serum IGF-I and BMI in women with BMI $\geq$ 26 kg/m^2 was statistically significant (beta coefficient=-0.014; P-value F-test<0.0001), but the positive apparent relationship of serum IGF-I and BMI in women with BMI<26 kg/m^2 was not (beta coefficient=0.0053; P-value F-test=0.31).

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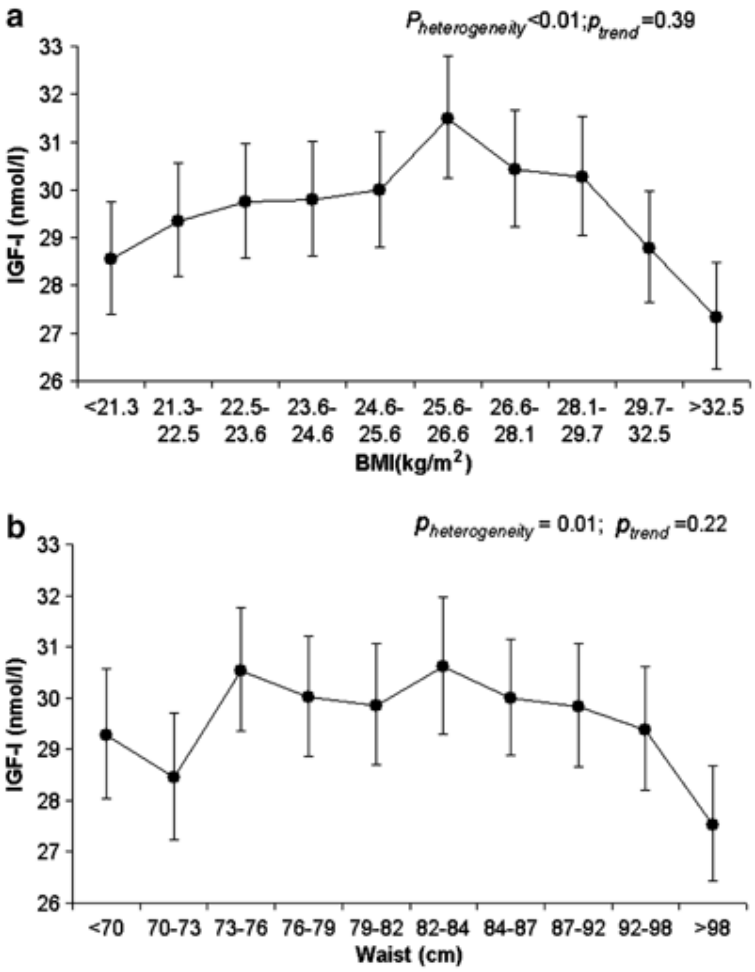
Figure 1.



Serum insulin-like growth factor-I (IGF-I) levels by deciles of body mass index (BMI) (**a**) and waist-circumference (**b**) in 2139 European women. Values are adjusted least-square means (95% confidence interval). Analysis of variance was used to test for differences in mean levels of IGF-I and insulin-like binding protein (IGFBP)-3. P-values for linear trend were estimated by modelling IGF-I measurements using the median value in each decile. Results are adjusted for age, and laboratory batch.

We examined the nonlinear relationship of waist circumference and serum IGF-I in the same way. A similar result was obtained when we then stratified the study population in two groups according to waist circumference higher or lower than 83 cm (Figure 1b). In the range of waist circumference values observed in this population, there was no relationship between the circumference and serum IGF-I when waist circumference was ≤83 cm (beta coefficient=0.0005; P-value F-test=0.77), while there is a significant inverse association of serum IGF-I with central obesity for waist circumferences higher than 83 cm (beta coefficient=-0.005; P-value F-test <0.0001).

IGF-binding protein-3 was significantly positively related with BMI, WHR and waist circumference. The relationship of IGFBP-3 with WHR and waist circumference persisted after adjustment for BMI, but the statistical significance of the relationship with BMI disappeared after adjustment for WHR.

The molar ratio IGF-I–IGFBP-3 tended to increase with increasing levels of BMI in non-obese women up to the 4th quintile of BMI, but the mean molar ratio was significantly lower in women in the 5th quintile of BMI (>29.7 kg/m^2), corresponding to overweight and obese women, compared to the other women. The statistical significance persisted after adjustment for WHR, but the linear trend did not persist ($P_{heterogeneity}<0.0001$, $P_{trend}=0.12$). The relationship of the molar ratio with waist circumference was similar to the relationship with BMI. Mean molar ratios were 0.249 and 0.255 in the 1st and 2nd quintile of waist circumference, while in women in the 3rd, 4th and 5th quintile (waist circumference over 79 cm) the relationship with the molar ratio was inversed. The molar ratio was inversely and linearly related to the WHR ($P_{heterogeneity}=0.02$, $P_{trend}=0.005$).

Discussion

In this large cross-sectional study, serum IGF-I levels were nonlinearly related to two measures of overall adiposity: BMI and waist circumference. These results are consistent with previous evidence of a nonlinear relationship between BMI and IGF-I. In a Swedish population of 445 men and 391 women[33] the highest levels of IGF-I were found at a BMI of about 24–26 kg/m^2 in both sexes, with the lowest hormone levels in the extreme categories of BMI, although the nonlinear relationship achieved statistical significance only among the men. In another study population comprising 620 women from Italy, Sweden and New York, the nonlinear relationship was observed among the 443 postmenopausal women; the highest IGF-I levels were observed among the women with a BMI of between 24 and 25 kg/m^2.[34] In a study of 292 British women, the BMI corresponding to the highest IGF-I level was between 26.0 and 27.9 kg/m^2, but the sample size was too small to achieve statistically significant heterogeneity.[35] The large cross-sectional study by Holmes et al.[31] (1037 women) also showed the highest mean level of IGF-I in women with BMI between 23 and 24.9 kg/m^2, although no formal tests were made for the existence of a nonlinear relationship. Finally, in the Multiethnic Cohort, women in the second quartile of BMI (i.e. 23.0–25.0 kg/m^2) had the highest level of IGF-I, with lower levels among women in the extreme categories of BMI.[36]

It has been hypothesized that the nonlinear relationship between increasing adiposity and circulating IGF-I levels is due to weight-related disruptions in insulin and GH secretion.[13, 45, 46] Prolonged fasting, as observed in patients with anorexia nervosa, and short-term fasting of normal-weight subjects, results in decreased IGF-I levels,[47, 48] and there is a stepwise increment of IGF-I values related to weight gain in anorexic patients.[49] Short-term overfeeding of normal-weight women also results in increased IGF-I levels.[50] In lean individuals, or after prolonged fasting, the comparatively low endogenous insulin production is associated with a reduction in GH receptor levels and resistance to the GH stimulation of IGF-I synthesis. Increasing insulin levels with increased BMI sensitizes liver (and probably other tissues) to the stimulatory effects of GH on IGF-I synthesis. In chronically hyperinsulinemic states, such as obesity, insulin inhibits the synthesis of IGFBP-1 and -2 and increases the free IGF-I fraction.[51, 52] Insulin also increases free circulating IGF-I by downregulating the synthesis of IGF-binding proteins-1 and -2 which, together with IGFBP-3, play an important role in regulating the free fraction of IGF-I. In turn, increased free IGF-I exerts a negative feedback on pituitary GH secretion, the primary stimulus for hepatic IGF-I synthesis and causes a decrease in total IGF-I levels.[53] Up to a certain level, increasing adiposity would increase IGF-I levels but, with further increases in adiposity, the increasing negative feedback of free IGF-I on GH secretion would gradually predominate and lead to a reduction in total circulating IGF-I levels.

In this study, there was a positive relationship between serum IGFBP-3 levels and WHR and waist circumference, while the association of IGFBP-3 levels with BMI, a measure of total adiposity, was no longer significant after adjustment for WHR, a measure of central adiposity. Results of previous studies are inconsistent. Some studies reported a small increase in IGFBP-3 with increasing obesity[27, 30, 35] but in other studies no relationship was observed.[29, 32, 34, 54, 55]

We observed lower means of the molar ratio IGF-I/IGFBP-3 in women with BMI>29.7 kg/m^2, with WHR >0.226 and with waist circumference >85 cm in this population, compared to other women. The mean molar ratios were lower in women in the lowest quintile of BMI (BMI<22.5 kg/m^2) compared to women in the next closest quintile. Only the free form of IGF-I is considered to be biologically active and cross the capillary boundaries to reach the target cells. It has been speculated that the molar ratio IGF-I/IGBP-3 could be considered a marker of free IGF-I.[56] Under this assumption, there must be a nonlinear relationship between adiposity and biologically active IGF-I, but the interpretation of our results is limited by the lack of measurement of IGFBP-1 and IGFBP-2, which also modulate IGF-1 bioactivity. The molar ratio was inversely related with central adiposity, measured as WHR. We could similarly speculate that biologically active IGF-I would be inversely related with central adiposity.

The strengths of the present study are its large size, which reduces the possibility that bias influenced our results, and the careful exclusion of women who were using exogenous hormones at the time of blood donation – a factor that can substantially influence IGF-I levels.[57, 58] In addition, we were able to investigate the relationship of IGF-I and IGFBP-3 with WHR, a measure of central adiposity, and to confirm our results on BMI in analyses using the waist circumference as a second indicator of obesity. Another strength of this study is the possibility to evaluate the role of main potential confounders. The results are based on a single measurement of IGF-I and IGFBP-3, but a single measurement of IGF-I and IGFBP-3 may be adequate to represent long-term circulating levels.[22] Our study is limited by its cross-sectional design, that did not allow us to examine the temporality of the association between anthropometric characteristics and serum IGF-I and IGFBP-3. Another limitation stems from the slight differences in protocols for measuring anthropometric indices and handling blood samples in the EPIC study. We adjusted all analyses for laboratory batch and centre to control for this heterogeneity. Finally, only women were included in this study.

In conclusion, our data confirm the nonlinear relationship of circulating IGF-I with BMI in women. This relationship is strongest with total obesity, measured as BMI and waist circumference, compared with the relationship of serum IGF-I with central obesity, measured as WHR. We observed a positive association of serum IGFBP-3 with the indicators of obesity, which was stronger for central obesity (WHR). Our results indicate that future studies should investigate whether the relationship of overweight and obesity with the risk of some cancers and other chronic diseases is partially explained by modifications of IGF-I bioavailability.

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