The Associations of Diet with Serum Insulin-like Growth Factor I and Its Main Binding Proteins in 292 Women Meat-Eaters, Vegetarians, and Vegans[1]

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Abstract

The lower rates of some cancers in Asian countries than in Western countries may be partly because of diet, although the mechanisms are unknown. The aim of this cross-sectional study was to determine whether a plant-based (vegan) diet is associated with a lower circulating level of insulin-like growth factor I (IGF-I) compared with a meat-eating or lacto-ovo-vegetarian diet among 292 British women, ages 20–70 years. The mean serum IGF-I concentration was 13% lower in 92 vegan women compared with 99 meat-eaters and 101 vegetarians ($P = 0.0006$). The mean concentrations of both serum IGF-binding protein (IGFBP)-1 and IGFBP-2 were 20–40% higher in vegan women compared with meat-eaters and vegetarians ($P = 0.005$ and $P = 0.0008$ for IGFBP-1 and IGFBP-2, respectively). There were no significant differences in IGFBP-3, C-peptide, or sex hormone-binding globulin concentrations between the diet groups. Intake of protein rich in essential amino acids was positively associated with serum IGF-I (Pearson partial correlation coefficient; $r = 0.27$; $P < 0.0001$) and explained most of the differences in IGF-I concentration between the diet groups. These data suggest that a plant-based diet is associated with lower circulating levels of total IGF-I and higher levels of IGFBP-1 and IGFBP-2.

Introduction

IGF[3] is a polypeptide hormone that stimulates cell proliferation and inhibits cell death. Experimental studies have shown IGF-I to promote the growth of both normal and malignant cells in breast tissue (1). Prospective epidemiological studies have shown that elevated levels of IGF-I, as absolute concentrations or relative to levels of IGFBP-3, are associated with an increased risk of breast cancer in premenopausal women (2, 3). The bioavailability of IGF-I *in vivo* is complex; although largely originating in the liver, it can also be produced locally in many tissues and can thus promote growth in an autocrine/paracrine manner as well as through endocrine pathways. Nevertheless, the serum concentration can be used as a marker of the main circulating store of IGF-I (4).

IGF-I and its main binding proteins are known to be sensitive to energy balance and other nutritional factors. Severe energy and protein restriction substantially reduces serum IGF-I concentration in both animals and humans (5) and may be one mechanism through which energy restriction reduces tumor growth (6). In particular, restriction of protein rich in essential amino acids substantially reduces IGF-I production *in vitro* (7) and *in vivo* (8), suggesting that certain essential amino acids are required to maximize IGF-I production. Independently of the effects of energy and protein restriction, zinc deficiency has also been associated with reduced IGF-I levels in both animals (9–12) and humans and which are normalized after zinc supplementation (13–15).

The effects of habitual diet on serum concentrations of IGF-I and its main binding proteins have not been studied in detail (16–18). We reported previously that vegan men had a significant 9% lower serum IGF-I concentration compared with meat-eaters and lacto-ovo-vegetarians (19), suggesting that nutritional factors specific to a plant-based diet may reduce IGF-I levels. The aim of this study is to examine the role of diet in relation to circulating levels of IGF-I among 292 women meat-eaters, vegetarians, and vegans. The associations between dietary intake and circulating levels of its three main binding proteins (IGFBP-1, IGFBP-2, and IGFBP-3) as well as C-peptide, a marker of pancreatic insulin secretion, and SHBG are also examined. In particular, we wanted to examine the hypotheses that high intakes of energy, protein rich in essential amino acids, and zinc are associated with high levels of IGF-I.

There has been some speculation that cow's milk, which naturally contains bovine IGF-I and is identical to human IGF-I, may increase circulating IGF-I levels (20) and thus may affect cancer risk (21). Indeed, two dietary intervention studies have found a dairy milk supplement to cause a 10% increase in serum IGF-I levels among adults (22) and children (23). A subsidiary aim of this study was, therefore, to examine whether increasing dairy milk consumption is associated with increasing IGF-I levels.

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[3] The abbreviations used are: IGF-I, insulin-like growth factor I; IGFBP, IGF-binding protein; SHBG, sex hormone-binding globulin; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food-frequency questionnaire; CI, confidence interval; BMI, body mass index.

Materials and Methods

Between 1993 and 1999, 58,000 individuals ages ≥20 years and living in the United Kingdom were recruited into the Oxford component of EPIC (24). Participants were recruited through collaborating general practitioners, vegetarian and vegan societies, health food magazines, and from friends and relatives of the participants. All participants completed a questionnaire that included details of age, anthropometric, smoking, and other lifestyle factors as well as a detailed semiquantitative FFQ.

A 30-ml nonfasting blood sample was obtained from ~30% of volunteers, on average 4 months after completion of the questionnaire. Whole blood was sent through the mail to the laboratory at ambient temperature, where it was immediately processed and stored in 0.5-ml aliquots of serum, plasma, erythrocytes, and buffy coat, using liquid sodium citrate as the anticoagulant for the plasma, erythrocytes, and buffy coat fractions. Samples were temporarily stored at −80°C for between 1 and 5 months until transportation to liquid nitrogen tanks, where they were stored at −196°C until analysis. All dates of blood sample and questionnaire processing, time of day at venipuncture, time since last meal at venipuncture, and medication taken on day of venipuncture were recorded.

This study includes a sample of 292 women recruited into EPIC-Oxford during 1994 and 1997 and comprises roughly equal numbers of women in each of five 10-year age groups from ages 20 to 70 years. To maximize the variation in nutrient intake, equal numbers of meat-eaters, vegetarians, and vegans were selected; vegetarians were defined as those who did not eat meat or fish but did consume dairy products and/or eggs, and vegans were defined as those who did not eat any animal products. Subjects were excluded if they had a self-reported history of cancer or diabetes or were taking oral contraception or hormone replacement therapy at the time of recruitment. Women who were pregnant at the time of questionnaire or blood collection were also excluded. In the FFQ, subjects were asked to state how frequently they ate each of a range of foods over the past year based on nine frequency categories, ranging from never or less than once a month to six or more times a day. These questions covered 130 foods and beverages and also allowed subjects to add food products that were not specified on the questionnaire. Data on milk intake were derived from questions on the FFQ regarding the type (full cream, semi-skimmed, skimmed, Channel Islands, dried milk, soya, and none) and quantity of milk consumed/day (none, ¼ pint, ½ pint, ¾ pint, 1 pint, and >1 pint).

Estimated daily nutrient intakes were calculated by multiplying the nutrient content of each food of a specific portion size by the frequency of consumption as stated on the FFQ (25). Average portion sizes were based on those designated by the Ministry of Agriculture, Fisheries and Food (26). A previous validation study found that nutrient intakes estimated from the FFQ were moderately correlated with estimates from 16-day weighed records, with correlations of 0.52 and 0.43 for energy and protein intake, respectively (27). Information on vitamin or other nutritional supplement usage was obtained either from forms completed on the day of venipuncture or, if this was unavailable, from the dietary questionnaire. The sum of dietary and supplement intake was then used to estimate total dietary zinc intake.

To examine the association between proteins high in essential amino acids and hormone levels, protein intake was divided into animal protein (that derived from meat, fish, dairy, egg and mixed animal, and plant sources), soya protein and other plant protein. Proteins derived from animal sources contain relatively higher amounts of essential amino acids than most plant sources, whereas soya contains a substantially higher quantity than other common plant proteins and is thus an important source of essential amino acids among vegans (28). The sum of animal plus soya protein was therefore used as an index of protein high in essential amino acids.

Serum aliquots for each subject were sent to the International Agency for Research on Cancer (Lyon, France) for analysis. Each assay batch included equal numbers of meat-eaters, vegetarians, and vegans selected at random and included two quality control samples; all measurements were carried out blinded to the subject's dietary group. Immunoassays were used to measure all peptide hormone concentrations (Diagnostic System Laboratory, Webster, TX), and the protocol for the IGF-I assay included an acid-ethanol extraction step to release IGF-I from its binding proteins. Detection limits for IGF-I, IGFBP-1, IGFBP-2, IGFBP-3, and C-peptide measurements were 0.004 nmol/liter, 0.013 nmol/liter, 1.6 nmol/liter, 1.4 nmol/liter, and 0.04 nmol/liter, respectively. Mean intra-and inter-batch coefficients of variation were 6.3 and 13.4%, respectively, for IGF-I, 3.8 and 16% for IGFBP-1, 8.2 and 16.8% for IGFBP-2, 12.9 and 11.4% for IGFBP-3, 7.2 and 18.3% for C-peptide, and 9.7 and 15.4% for SHBG.

Statistical Analysis. Serum concentrations of IGF-I, IGFBP-3, IGF-I:IGFBP-3 ratio, IGFBP-1, and SHBG were natural logarithmically transformed, and IGFBP-2 and C-peptide were square root transformed to approximate normal distributions. The associations between diet group and serum peptides were analyzed using ANOVA, and the mean concentrations and their corresponding 95% CIs are presented as back-transformed values. All multivariate analyses presented here are adjusted for age (20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, and 65–70) and for variables associated with blood collection and analysis: time of day at venipuncture (<09.30, 09.30–10.44, 10.45–13.29, and 13.30+); time since last meal at venipuncture (<1.15, 1.15–1.59, 2.00–3.29, 3.30+ h); days between venipuncture and blood processing (1, 2, 3, and 4+ days); assay batch (1, 2, 3, and 4). Where appropriate, additional adjustment for quartiles of BMI (<20.4, 20.4–22.0, 22.1–24.1, 24.2+ kg/m^2) was made; inclusion of other lifestyle and reproductive factors did not alter the models for any analytes and were not included in the final analysis. All *P*s refer to tests of heterogeneity between the group means, using the F statistic from the ANOVA table, unless otherwise stated. A $P < 0.05$ was considered statistically significant, except in the analysis of nutrients and hormone concentrations, and all significance tests were two-sided.

Nutrients were natural logarithmically transformed and adjusted for energy intake using the method described by Willett and Stampfer (29). Briefly, each nutrient was entered as the dependent variable in a regression model, with total energy intake as the independent variable. The residuals from this model were then added to the expected nutrient value for the mean level of energy intake in the sample to arrive at an adjusted nutrient intake. All energy-adjusted nutrients were then subsequently added to the model as continuous variables and were analyzed using Pearson's partial correlation coefficients. All models were additionally adjusted for the natural logarithm of total energy intake; no adjustment was made for diet group. Separate analyses for each dietary variable were conducted because of the intercorrelation of the nutrient variables and because of the multiplicity of comparisons; a $P < 0.01$ was considered statistically significant. To examine the extent to which each nutrient intake explained the differences in

Table 1 Anthropometric and dietary characteristics of 292 women meat-eaters, vegetarians, and vegans

Arithmetic means and SDs

Variable	Meat-eaters (n = 99)	Vegetarians (n = 101)	Vegans (n = 94)	Test of heterogeneity
Nondietary variables				
Age (yr)	45 (14.0)	44 (13.8)	44 (12.8)	0.689
Height (cm)	164 (6.31)	163 (5.39)	163 (6.53)	0.370
Weight (kg)	62.2 (9.17)	59.7 (7.99)	58.6 (6.53)	0.013
BMI (kg/m^2)	23.1 (3.27)	22.5 (2.91)	22.0 (3.01)	0.039
Dietary variables				
Energy (MJ/day)	8.29 (2.81)	7.79 (2.25)	7.42 (2.06)	0.092
Protein (% energy)	17.6 (3.29)	13.7 (2.28)	13.5 (2.04)	<0.0001
Animal protein[a] (% energy)	10.9 (3.68)	4.81 (2.18)	0	<0.0001
Soya protein (% energy)	0.24 (0.46)	1.05 (1.14)	3.11 (1.96)	<0.0001
Animal plus soya protein (% energy)	11.1 (3.55)	5.86 (2.07)	3.11 (1.96)	<0.0001
Nonsoya plant protein (% energy)	6.50 (1.40)	7.84 (1.69)	10.4 (1.73)	<0.0001
Carbohydrate (% energy)	49.2 (6.74)	52.4 (6.53)	53.8 (6.91)	<0.0001
Total fat (% energy)	30.6 (6.29)	31.1 (6.40)	30.6 (7.08)	0.826
Saturated fatty acids (% energy)	9.74 (3.39)	8.92 (3.66)	5.37 (2.01)	<0.0001
Monounsaturated fatty acids (% energy)	9.24 (2.63)	8.45 (2.81)	8.42 (3.13)	0.077
Polyunsaturated fatty acids (% energy)	4.91 (1.71)	5.73 (2.04)	8.10 (2.95)	<0.0001
Alcohol (% energy)	2.67 (3.37)	2.75 (3.44)	2.12 (3.25)	0.368
P:S ratio	0.56 (0.25)	0.71 (0.32)	1.61 (0.36)	<0.0001
Cholesterol (mg/day)	211 (123)	109 (68.9)	~0[b]	<0.0001
Starch (g/day)	117 (47.7)	127 (47.7)	138 (46.0)	0.0006
Total sugars (g/day)	133 (54.7)	123 (40.4)	106 (41.7)	<0.0001
Non-starch polysaccharides (g/day)	20.9 (8.41)	23.4 (8.31)	27.9 (10.8)	<0.0001
Zinc (mg/day)[c]	10.6 (5.03)	9.49 (5.57)	10.0 (5.91)	0.366

[a] Animal protein is protein derived from meat, fish, dairy, egg and mixed animal and plant protein sources.
[b] Cholesterol intake among vegans is negligible.
[c] Includes intake from supplements.

hormone concentration between the diet groups, each nutrient was included in the model as a categorical variable, categorized according to its quartile distribution, together with the natural logarithm of total energy intake. All statistical analyses were performed using Stata version 7.0 (30).

Results

Anthropometric and dietary characteristics of each diet group are shown in Table 1. Vegetarians and vegans had a lower weight and BMI than meat-eaters, with vegan women weighing an average 3.6 kg less than meat-eaters and 1.1 kg less than vegetarians. As expected, nutrient intakes differed significantly between the diet groups. Vegetarians and vegans had significantly lower intakes of energy, protein, animal plus soya protein, saturated fatty acids (each as percentage of energy), and lower intakes of dietary cholesterol and total sugars compared with meat-eaters. Conversely, vegans had higher intakes of carbohydrate, nonsoya plant protein, polyunsaturated fatty acids (each as percentage of energy), polyunsaturated:saturated fatty acid ratio, nonstarch polysaccharides, and starch than meat-eaters; vegetarians had intermediate values for these nutrient intakes. Daily intakes of energy, total fat, monounsaturated fatty acid, alcohol intake (each as a percent energy), and zinc intake were not significantly different between diet groups.

Associations between Time of Blood Collection and Hormone Concentrations. The association between age and anthropometric, lifestyle, and reproductive factors and circulating concentrations of IGF-I and its main binding proteins are reported elsewhere.[4] The associations between time of day and time since last meal at venipuncture and hormone concentrations are presented in Table 2. Although total IGF-I concentration was not associated with time of day at venipuncture, IGFBP-1 and IGFBP-3 concentration was 41 and 10% lower, respectively, among women whose blood was collected after 13.30 h compared with women whose blood was taken before 9.30 h (test for linear trend; $P < 0.0001$ and 0.016 for IGFBP-1 and IGFBP-3, respectively). In contrast, SHBG concentration was 27% higher among women whose blood was taken in the afternoon compared with women whose blood was taken in the early morning (test for linear trend; $P = 0.022$). C-peptide concentration also varied significantly with time of day at venipuncture, being lowest in women whose blood was taken during the late morning and higher in the early morning and early afternoon (test for heterogeneity; $P = 0.005$). This is most likely a reflection of food intake and corresponds with the 50% lower C-peptide concentration found among women whose blood was collected 3.5 h or more after eating compared with women who gave blood <75 min after eating (test for linear trend; $P < 0.0001$). IGFBP-1 also varied significantly with time since last meal at venipuncture and was lowest among women whose blood was taken between 2 and 3.5 h after eating and highest among those who had fasted for more than 3.5 h (of which the mean was 8 h; test for heterogeneity; $P < 0.0001$). Days between venipuncture and blood processing was not associated with IGF-I or its main binding proteins, although C-peptide concentration was 45% lower in women whose blood samples took 4 days or more to be processed compared with samples that took 1 day (test for linear trend; $P < 0.0001$).

[4] N. E. Allen, P. N. Appleby, R. Kaaks, S. Rinaldi, G. K. Davey, and T. J. Key. The lifestyle determinants of serum insulin-like growth-factor I (IGF-I) and its main binding proteins in British women, submitted for publication.

Table 2 Adjusted mean hormone concentrations (nmol/liter) by time of day and time since last meal at venipuncture, days between venipuncture, and blood processing[a]

Variable	Nos.	IGF-I	IGFBP-1	IGFBP-2	IGFBP-3	C-peptide	SHBG
Time of day at venipuncture							
<9.30	72	31.4 (29.3–33.6)	1.25 (1.03–1.51)	11.8 (10.1–13.7)	153 (146–160)	0.82 (0.73–0.91)	47.7 (42.1–53.8)
9.30–10.44	74	29.0 (27.2–30.9)	1.13 (0.94–1.35)	13.6 (11.9–15.4)	142 (136–149)	0.83 (0.75–0.92)	50.7 (45.1–56.9)
10.45–13.29	72	29.3 (27.4–31.3)	1.01 (0.84–1.22)	14.5 (12.6–16.4)	144 (137–151)	0.72 (0.64–0.80)	51.4 (45.6–57.9)
13.30+	74	29.4 (27.5–31.4)	0.74 (0.61–0.89)	13.3 (11.6–15.2)	137 (131–144)	0.93 (0.84–1.03)	60.6 (52.7–68.3)
Heterogeneity/linear		0.382/0.247	0.0001/0.0001	0.158/0.416	0.032/0.016	0.005/0.154	0.108/0.022
Time since last meal at venipuncture (hrs·min)							
<1.15	73	29.0 (27.2–30.9)	1.25 (1.04–1.50)	12.4 (10.8–14.2)	145 (139–152)	1.12 (1.02–1.23)	53.2 (47.3–59.8)
1.15–1.59	76	30.9 (29.0–33.0)	0.89 (0.75–1.07)	12.6 (11.0–14.4)	142 (136–149)	0.93 (0.84–1.02)	48.5 (43.2–54.4)
2.00–3.29	69	30.6 (28.6–32.8)	0.71 (0.59–0.86)	14.6 (12.7–16.6)	147 (140–154)	0.75 (0.67–0.84)	51.4 (45.4–58.2)
3.30+	74	28.5 (26.7–30.4)	1.32 (1.10–1.58)	13.7 (11.9–15.5)	142 (135–148)	0.55 (0.48–0.62)	56.7 (50.5–64.8)
Heterogeneity/linear		0.305/0.543	0.0001/0.801	0.158/0.212	0.642/0.568	0.0001/0.0001	0.310/0.357
Time between venipuncture and blood processing (days)							
1	164	29.9 (28.7–31.2)	1.04 (0.92–1.17)	13.6 (12.4–14.8)	143 (139–147)	0.95 (0.89–1.00)	52.5 (48.6–56.8)
2	79	29.4 (27.6–31.3)	0.95 (0.80–1.14)	12.7 (11.1–14.5)	143 (138–151)	0.75 (0.67–0.84)	51.1 (45.6–57.3)
3	29	29.8 (26.9–33.2)	1.05 (0.78–1.41)	13.1 (10.3–16.1)	148 (138–160)	0.60 (0.49–0.73)	52.3 (43.0–63.5)
4+	20	29.4 (26.0–33.3)	1.00 (0.71–1.42)	13.6 (10.4–17.2)	145 (133–158)	0.52 (0.40–0.66)	55.5 (44.4–69.4)
Heterogeneity/linear		0.957/0.689	0.948/0.651	0.957/0.612	0.832/0.543	0.0001/0.0001	0.978/0.917

[a] Values are adjusted for each other and age group (10 categories), BMI group (4 categories), diet group (3 categories), and assay batch (4 categories).

Table 3 Mean serum hormone concentrations (nmol/liter) in 292 women meat-eaters, vegetarians, and vegans[a]

Back-transformed means with 95% CIs (in parentheses).

Hormone (nmol/liter)	Meat-eaters (n = 99)	Vegetarians (n = 101)	Vegans (n = 92)	Test of heterogeneity
IGF-I	30.9 (29.3–32.7)	31.2 (29.5–32.9)	27.0 (25.5–28.6)	0.0006
IGFBP-1	0.91 (0.78–1.07)	0.90 (0.77–1.06)	1.28 (1.08–1.51)	0.005
IGFBP-2	11.2 (9.79–12.7)	13.2 (11.7–14.9)	15.8 (14.0–17.6)	0.0008
IGFBP-3	148 (142–154)	140 (135–146)	144 (138–150)	0.171
IGF-I:IGFBP-3 ratio	0.21 (0.20–0.22)	0.22 (0.21–0.23)	0.19 (0.18–0.20)	0.0001
C-peptide	0.83 (0.76–0.90)	0.87 (0.80–0.95)	0.76 (0.69–0.83)	0.236
SHBG	51.7 (46.6–57.4)	50.9 (45.9–56.5)	54.7 (49.1–61.0)	0.624

[a] Values are adjusted for age (10 categories), assay batch (4 categories), time of day at venipuncture (4 categories), time since last meal at venipuncture (4 categories), and time between venipuncture and blood processing (4 categories). Insufficient serum led to IGF-I and IGFBP-3 measurement being unavailable in 1 subject and SHBG in 2 subjects.

Associations between Diet Group and Hormone Concentrations. Mean hormone concentrations in each diet group are shown in Table 3 after adjustment for age and variables associated with blood collection and handling, although these factors did not appreciably alter the unadjusted values (data not shown). Vegan women had a 13% lower mean serum IGF-I concentration than both meat-eaters ($P = 0.001$) and vegetarians ($P = 0.0006$). The mean molar ratio of IGF-I:IGFBP-3 (the concentration of IGF-I relative to its main binding protein) was also significantly lower in vegans than in meat-eaters ($P = 0.005$) and in vegetarians ($P < 0.0001$). The mean serum IGFBP-1 concentration was 41% higher in vegans than in both meat-eaters ($P = 0.005$) and vegetarians ($P = 0.004$). Serum IGFBP-2 concentration was also 41% higher in vegans than in meat-eaters ($P = 0.0002$) and 20% higher than in vegetarians ($P = 0.042$). The differences in mean hormone concentrations between diet groups were similar after additional adjustment for BMI was made, with the exception of IGFBP-1, where BMI reduced some but not all of the difference between the diet groups (test for heterogeneity; $P = 0.011$; Table 5). There were no significant differences in serum IGFBP-3, C-peptide, or SHBG concentrations between the diet groups, either before or after adjustment for BMI.

Associations between Nutrients and Peptide Hormones. The associations between nutrient intake and peptide hormone concentrations are shown in Table 4 after adjustment for potential confounders. Animal plus soya protein intake, a marker of protein high in essential amino acids across all diet groups, was the nutrient most strongly associated with serum IGF-I levels ($r = 0.27$; $P < 0.0001$). This corresponded to a significant 13% higher IGF-I concentration in the highest quartile of animal plus soya protein intake (≥41.5 g/day) compared with the lowest quartile (<16.2 g/day; test for linear trend; $P = 0.001$). In contrast, nonsoya plant protein, a marker of protein low in essential amino acids, was negatively correlated with IGF-I ($r = -0.17$; $P = 0.006$) and positively correlated with IGFBP-1 and IGFBP-2 ($r = 0.20$; $P = 0.001$ for both IGFBP-1 and IGFBP-2). Although soya protein was not correlated with IGF-I concentration in the population as a whole ($r = -0.04$), soya protein intake was significantly associated with serum IGF-I concentration among vegan women ($r = 0.29$; $P = 0.016$).

Zinc intake was not associated with IGF-I but was significantly positively correlated with IGFBP-1 concentration ($r = 0.20$; $P = 0.001$). This corresponded to a significant 38% higher IGFBP-I concentration in the highest quartile of zinc intake (≥9.78 mg/day) compared with the lowest quartile (<7.24 mg/day; test for linear trend; $P = 0.016$). Zinc intake was not associated with IGFBP-2 or IGFBP-3 levels.

Because IGF-I was highly correlated with IGFBP-3 (Pear-

Table 4 Pearson partial correlation coefficients between nutrients and hormones[a]

Nutrient	IGF-I	IGFBP-1	IGFBP-2	IGFBP-3	C-peptide	SHBG
Energy	0.05	−0.11	0.04	−0.02	−0.01	−0.08
Total protein	0.08	0.07	−0.10	0.06	−0.07	0.03
Animal protein[b]	0.18[c]	−0.14	−0.15[c]	−0.01	0.05	−0.03
Soya protein	−0.04	0.03	0.10	0.04	−0.05	0.04
Animal plus soya protein	0.27[d]	−0.07	−0.15	0.10	0.00	−0.04
Nonsoya plant protein	−0.17[c]	0.20[c]	0.20[d]	−0.04	−0.05	0.06
Carbohydrate	0.05	0.16	0.04	0.05	0.08	−0.02
Total fat	−0.03	−0.14	−0.02	−0.04	−0.02	−0.01
Saturated fatty acids	0.14	−0.22[d]	−0.15	0.02	0.05	−0.06
Monounsaturated fatty acids	−0.05	−0.14	−0.05	−0.03	−0.05	−0.01
Polyunsaturated fatty acids	−0.08	−0.04	0.07	0.00	−0.03	−0.01
Alcohol	0.01	−0.04	−0.01	0.03	−0.02	0.06
P:S ratio	−0.15	0.13	0.15	−0.04	−0.09	0.03
Cholesterol	0.15	−0.13	−0.14	−0.03	0.02	−0.03
Starch	−0.05	0.13	0.07	−0.02	−0.04	0.01
Total sugars	0.15	0.08	−0.04	0.05	0.13	−0.04
Non-starch polysaccharides	−0.17[c]	0.21[d]	0.20[d]	−0.11	−0.10	0.09
Zinc[e]	−0.04	0.20[d]	−0.05	0.04	−0.02	0.09

[a] Values are adjusted for age (10 categories), BMI (4 categories), assay batch (4 categories), time of day at venipuncture (4 categories), time since last meal at venipuncture (4 categories), days between venipuncture and processing (4 categories), and (ln)total energy.
[b] Animal protein is protein derived from meat, fish, dairy, egg, and mixed animal and plant protein sources.
[c] $P \leq 0.01$.
[d] $P \leq 0.001$.
[e] Includes intake from supplements.

Table 5 Mean concentration of IGF-I, IGFBP-1 and IGFBP-2 by diet group after additional adjustment for selected nutrients

Back-transformed means with 95% CIs (in parentheses).

Adjustments	Meat-eaters	Vegetarians	Vegans	Test for heterogeneity
IGF-I[a]	30.8 (29.1–32.6)	31.3 (29.6–33.0)	27.1 (25.5–28.7)	0.0007
Animal plus soya protein	30.3 (27.8–33.1)	30.5 (28.7–32.4)	28.3 (26.1–30.7)	0.325
Nonsoya plant protein	30.4 (28.5–32.5)	31.2 (29.5–33.0)	27.5 (25.6–29.6)	0.036
Saturated fat	30.9 (29.1–32.8)	31.2 (29.5–33.1)	27.0 (25.2–29.0)	0.011
Nonstarch polysaccharides	30.7 (29.0–32.6)	31.4 (29.7–33.1)	27.1 (25.4–28.8)	0.002
IGFBP-1[a]	0.96 (0.82–1.12)	0.89 (0.76–1.04)	1.24 (1.05–1.46)	0.011
Animal plus soya protein	0.99 (0.75–1.24)	0.89 (0.75–1.06)	1.23 (0.98–1.54)	0.073
Nonsoya plant protein	1.07 (0.89–1.29)	0.89 (0.76–1.04)	1.10 (0.90–1.34)	0.136
Saturated fat	1.06 (0.90–1.25)	0.94 (0.80–1.10)	1.05 (0.86–1.27)	0.522
Nonstarch polysaccharides	1.03 (0.87–1.21)	0.89 (0.76–1.04)	1.14 (0.96–1.36)	0.118
Zinc	0.94 (0.80–1.10)	0.91 (0.78–1.06)	1.23 (1.04–1.45)	0.021
IGFBP-2[a]	11.7 (10.3–13.2)	13.0 (11.6–14.6)	15.4 (13.8–17.2)	0.0049
Animal plus soya protein	13.4 (11.1–16.0)	12.6 (11.0–14.3)	13.9 (11.7–16.2)	0.600
Nonsoya plant protein	11.9 (10.3–13.7)	13.1 (11.7–14.7)	15.0 (13.0–17.2)	0.154
Saturated fat	11.7 (10.2–13.3)	13.1 (11.6–14.7)	15.4 (13.4–17.5)	0.038
Nonstarch polysaccharides	11.8 (10.3–13.4)	13.0 (11.5–14.5)	15.3 (13.5–17.2)	0.029

[a] Values are adjusted for age (10 categories), BMI (4 categories), assay batch (4 categories), time of day at venipuncture (4 categories), time since last meal at venipuncture (4 categories), days between venipuncture and processing (4 categories), and (ln)total energy intake.

son's correlation coefficient, $r = 0.56$) and IGF-I:IGFBP-3 (Pearson's correlation coefficient, $r = 0.79$), the IGF-I:IGFBP-3 molar ratio showed similar associations to that of total IGF-I, being significantly positively correlated with animal protein and animal plus soya protein and significantly negatively correlated with nonsoya plant protein (data not shown). No nutrients were significantly associated with IGFBP-3, C-peptide, or SHBG concentrations.

We then examined which of the nutrients that were significantly correlated with IGF-I and IGFBP-1 and IGFBP-2 concentrations might account for the differences in peptide hormones observed between the diet groups (Table 5). For IGF-I, adjustment for animal plus soya protein reduced the range of mean adjusted IGF-I levels between meat-eaters and vegans by 46%, and the differences between diet groups were no longer statistically significant (test for heterogeneity; $P = 0.325$). Adjustment for nonsoya plant protein reduced the differences between meat-eaters and vegans by 22%, although the differences between diet groups remained statistically significant (test for heterogeneity; $P = 0.036$). Adjustment for saturated fat or nonstarch polysaccharides did not appreciably alter the differences in IGF-I concentration between the diet groups.

For IGFBP-1, individual adjustments for animal plus soya protein, nonsoya plant protein, saturated fat, and nonstarch polysaccharides were all associated with a reduction in differences in mean values, and the differences between the diet

Table 6 Mean IGF-I concentration (nmol/liter) by dairy or soya milk intake in each dietary group[a]

Back-transformed means with 95% CIs (in parentheses).

Daily milk intake	Meat-eater: dairy milk		Vegetarian: dairy milk		Vegan: soya milk	
	Nos.	IGF-I	Nos.	IGF-I	Nos.	IGF-I
None	3	30.1 (22.1–41.9)	9	25.7 (21.4–30.9)	9	23.2 (18.2–29.6)
¼ pint	25	31.1 (26.9–36.0)	37	30.6 (28.0–33.5)	48	25.8 (23.5–28.3)
½ pint	38	30.8 (27.9–34.0)	35	33.5 (30.5–36.8)	21	29.5 (25.4–34.4)
>¾ pint	19	30.7 (27.4–34.5)	20	30.7 (27.1–34.8)	14	29.8 (24.5–36.2)
Test for linear trend		$P = 0.834$		$P = 0.121$		$P = 0.054$

[a] Values are adjusted for age (10 categories), BMI (4 categories), assay batch (4 categories), time of day at venipuncture (4 categories), time since last meal at venipuncture (4 categories), days between venipuncture and processing (4 categories), and (ln)total energy intake.

groups were no longer significant (Table 5). Saturated fat intake was the nutrient most strongly associated with IGFBP-1 and largely eliminated the difference in mean IGFBP-1 concentration between meat-eaters and vegans, with vegetarians having the lowest values (test for heterogeneity between the diet groups; $P = 0.522$). Zinc intake did not appreciably alter the differences in IGFBP-I concentration between the diet groups.

The effect of nutrient intake on IGFBP-2 was similar to that observed for IGF-I. Individual adjustment for animal plus soya protein and nonsoya plant protein reduced the differences in IGFBP-2 concentration between meat-eaters and vegans by 86% and 16%, respectively, and the differences between diet groups were no longer significant (tests for heterogeneity; $P = 0.600$ and 0.154 for animal plus soya protein and nonsoya plant protein, respectively). Adjustment for saturated fat and nonstarch polysaccharides made little difference to the mean IGFBP-2 concentration in each diet group.

Milk Intake and IGF-I Concentration. Increasing dairy milk intake was not significantly associated with increasing serum IGF-I concentration in meat-eaters or vegetarians (Table 6) or among both groups combined (data not shown). However, vegan women who consumed ¾ pint or more of soya milk/day had a significant 28% higher IGF-I concentration than vegan women who did not drink soya milk.

Discussion

This is the first cross-sectional study to compare serum IGF-I and its main binding proteins in women meat-eaters, vegetarians, and vegans and the largest study to investigate the association between nutrient intake and IGF-I levels. Because of the associations found between time of day and time since last meal at venipuncture and IGFBP-1 concentration and between days in the mail and C-peptide concentration, all analyses presented here are adjusted for these factors. Indeed, it is well established that IGFBP-1 is highly sensitive to food intake increasing during an overnight fast and rapidly falling after food intake (31). However, adjustment for these variables made little difference to the estimates, suggesting that the nonfasting status of the women at the time of blood collection did not unduly influence the results. Nevertheless, some caution may be required in the interpretation of the associations for IGFBP-1 because this hormone is highly sensitive to food intake. Although these results are based on single samples, one measurement of serum IGF-I and its main binding proteins is thought to reliably reflect the mean annual concentration at least in middle-aged men, with Spearman correlation coefficients of 0.62–0.87 between two serum samples 1 year apart (32).

The main finding of this study is that total IGF-I levels were significantly 13% lower in vegan women compared with meat-eaters and vegetarians, a finding very similar to that reported in men from this cohort (19). Perhaps of equal importance is the finding that IGFBP-1 and IGFBP-2 concentrations (not measured among men) were ~40% higher in vegan women than in meat-eaters and vegetarians. Although the relationship between IGF-I and its binding proteins is not completely understood, it is thought that an increase in IGFBP-1 and IGFBP-2 concentrations may lead to an increased binding of IGF-I, thus reducing the proportion of IGF-I that is available to enter tissues (33).

Overall, these data support the hypothesis that nutritional factors specific to a vegan diet may reduce circulating levels of total and bioavailable IGF-I. Furthermore, these associations do not appear to be because of differences in body weight or other lifestyle characteristics between the diet groups. However, it is difficult to identify which nutrients are of importance because of the high correlations between nutrient intakes and dietary group. As expected, nutrient intakes characteristic of a vegan diet such as a low intake of saturated fat and a high intake of nonstarch polysaccharides and nonsoya plant protein were also associated with a low IGF-I and a high IGFBP-1 and IGFBP-2 concentration. Nevertheless, there are several known mechanisms through which nutritional components of a vegan diet may reduce IGF-I and increase IGFBP-1 and IGFBP-2, the most established of which is the effect of essential amino acid restriction. Vegan diets tends to be low in certain essential amino acids, and dietary restriction of one or more essential amino acids has been shown to reduce IGF-I and increase IGFBP-1 and IGFBP-2 production in animal (8, 34) and human feeding studies (35, 36). This may be attributable to an indirect effect of protein restriction in reducing growth hormone secretion and, hence, reducing IGF-I and increasing IGFBP-2 production (37) or a more direct effect of amino acid restriction in increasing IGFBP-1 production in hepatocytes (34, 38).

Indeed, intake of animal plus soya protein, used as an index of protein high in essential amino acids across all diet groups, was moderately positively correlated with IGF-I and negatively correlated with IGFBP-2 and, to a lesser extent, IGFBP-1. Conversely, a high intake of nonsoya plant protein, which is relatively low in essential amino acids, was moderately negatively correlated with IGF-I and positively correlated with IGFBP-1 and IGFBP-2. Furthermore, adjustment for either animal plus soya protein or nonsoya plant protein intake substantially reduced the differences in IGFBP-2 and, to a lesser extent, IGF-I and IGFBP-1 between the diet groups. Finally, the observation that increasing soya milk intake among vegans was associated with an increasing IGF-I concentration further suggests that essential amino acid intake may be an important determinant of IGF-I levels in vegans.

Another mechanism through which a vegan diet may influence IGFBP-1 levels is via an enhanced insulin sensitivity. A diet low in saturated fat and high in dietary fiber and complex carbohydrates may reduce insulin secretion, both directly by reducing the postprandial glycaemic response (39, 40), and indirectly by reducing adiposity (41), causing a large increase in the production of IGFBP-1 within the liver (42). Low intakes of saturated fat and nonstarch polysaccharides were each significantly correlated with IGFBP-1 concentration ($r = -0.22$ and -0.21, respectively) and indeed, saturated fat appeared to explain some of the observed difference in IGFBP-1 concentration between the diet groups. However, C-peptide concentration, used as a marker of insulin secretion, was similar among the diet groups, and additional adjustment for BMI had no effect on the association between diet group and IGFBP-1 concentration. It therefore remains unclear whether the differences in IGFBP-1 between the diet groups are attributable to an effect of essential amino acids or to differences in insulin sensitivity.

Previous data on the associations between dietary intake and IGF-I levels are sparse. Consistent with our data, other cross-sectional studies have also found no association between total protein intake and serum age-adjusted IGF-I levels in men (17, 18) or women (16). However, these studies have not investigated the effects of different types of protein intake on serum IGF-I and its main binding proteins.

Although it is well established that severe dietary restriction to 50–70% of energy requirements reduces circulating IGF-I concentration (43, 44), we and others have found no evidence that increasing energy intake, at least in the normal range, is associated with higher IGF-I levels (45). We also found no evidence that zinc intake is positively associated with IGF-I concentration, despite the wide range of intake. This is in contrast with a cross-sectional study of 119 United States postmenopausal women that found zinc intake to be the strongest nutritional determinant of IGF-I levels, with a correlation coefficient of 0.30 (16). We did find that zinc intake was positively associated with IGFBP-1 concentration, although it did not explain the differences in IGFBP-1 levels between the diet groups. As this was not an *a priori* hypothesis and there is no known mechanism through which zinc might stimulate IGFBP-1 production independent of that of IGF-I or the other IGFBPs, this finding should be interpreted with caution and may be because of chance.

We found no evidence to suggest that increasing dairy milk intake is associated with increasing IGF-I levels among meat-eaters and vegetarians. This is in contrast with other studies in which milk intake has been associated with a significant increase in circulating IGF-I levels among healthy middle-aged men and women (22, 46). However, there may have been insufficient heterogeneity in milk intake among the milk consumers to detect a significant association.

In summary, these results suggest that total IGF-I concentration is lower among women who adopt a vegan diet. In addition, IGFBP-1 and IGFBP-2 concentrations are substantially higher in vegan women compared with meat-eaters and vegetarians, suggesting that the amount of bioavailable IGF-I may be lower in vegan women. The nutritional characteristics of the vegan diet that account for these differences are not clear but may be related to vegans' lower intake of protein high in essential amino acids. These results suggest that even when total protein intake is not notably low, a low intake of essential amino acids, as typically found in a plant-based diet, may be sufficient to reduce serum IGF-I and increase serum IGFBP-1 and IGFBP-2 levels. Although these effects are relatively small, they could be of physiological importance as a relatively high circulating IGF-I concentration has been associated with an increased risk of breast cancer in premenopausal women (2, 3). There are, as yet, very limited data on cancer rates among vegan women (47) and work is needed to investigate whether individuals who follow such a diet may be at lower risk of breast cancer. However, the ecological observation that breast cancer incidence is lower in Asian countries where people follow a predominately plant-based diet lends support to the hypothesis that a plant-based diet may be associated with a lower risk of cancer via its effect on IGF-I availability.

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The Associations of Diet with Serum Insulin-like Growth Factor I and Its Main Binding Proteins in 292 Women Meat-Eaters, Vegetarians, and Vegans

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