

Association of diet with serum insulin-like growth factor I in middle-aged and elderly men¹⁻³

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ABSTRACT

Background: Insulin-like growth factor I (IGF-I) has been implicated in several chronic diseases, including cancer, heart disease, and osteoporosis.

Objective: Our aim was to assess whether intakes of total energy, alcohol, vitamins, minerals, and foods rich in protein and minerals (including red meat, fish and seafood, poultry, and milk) are associated with serum IGF-I concentrations in middle-aged and elderly men.

Design: We measured serum IGF-I concentrations in 226 free-living healthy men aged 42–76 y. The average of fourteen 24-h dietary telephone interviews performed over 1 y was used to estimate long-term dietary intake.

Results: We observed statistically significant positive associations between intakes of protein (P for trend = 0.001) and zinc (P for trend = 0.002) and serum IGF-I concentrations after adjusting for age. The difference in mean IGF-I concentrations for the highest compared with the lowest quintile of intake was $\approx 17\%$ (162 $\mu\text{g/L}$ compared with 139 $\mu\text{g/L}$) for protein and $\approx 16\%$ (166 $\mu\text{g/L}$ compared with 143 $\mu\text{g/L}$) for zinc. Consumption of red meat (P for trend = 0.05) and fish and seafood (P for trend = 0.07) was modestly positively associated with IGF-I concentrations. Other dietary factors were not associated with IGF-I concentrations.

Conclusion: In this population of healthy well-nourished men, greater dietary intakes of protein, zinc, red meat, and fish and seafood were associated with higher IGF-I concentrations. *Am J Clin Nutr* 2005;81:1163–7.

KEY WORDS Diet, insulin-like growth factor I, IGF-I, fish, minerals, nutrients, protein, red meat, zinc

INTRODUCTION

Accumulated epidemiologic evidence indicates that high circulating concentrations of insulin-like growth factor I (IGF-I) may increase the risk of various cancers, including prostate cancer, premenopausal breast cancer, and possibly colorectal cancer (1). Conversely, low IGF-I concentrations have been implicated in the development of osteoporosis (2–4), heart disease (5–7), and glucose intolerance (8). Thus, given the pivotal roles of IGF-I in health and disease and because few modifiable determinants of IGF-I concentrations have been identified, potential dietary associations are of great clinical interest.

It is well recognized that severe energy and protein deprivation is associated with lower IGF-I concentrations in animals and malnourished children (9–11). Animal data further suggest that specific minerals, including potassium, magnesium, and zinc,

are needed for optimal IGF-I synthesis and for anabolic effects (11). Nevertheless, despite evidence from animal studies and malnourished children, the potential role of dietary factors as predictors for circulating IGF-I concentrations in well-nourished adults has not been investigated with a detailed dietary assessment method. Epidemiologic studies have attempted to measure the association between diet and IGF-I concentrations with the use of dietary food-frequency questionnaires (12–20). To our knowledge, no previous study has used more detailed dietary assessment methods to assess associations of dietary intake with IGF-I concentrations in healthy men. Therefore, the objective of this study was to examine intake of total energy, alcohol, vitamins, minerals, and foods rich in protein and minerals (including red meat, fish and seafood, poultry, and milk) in relation to serum IGF-I concentrations in free-living middle-aged and elderly men who participated in fourteen 24-h dietary telephone interviews.

SUBJECTS AND METHODS

Study population

Details of this study have been described elsewhere (21). Briefly, the study population for this investigation was 226 free-living healthy men aged 42–76 y, who were randomly selected from the population register of Uppsala (city) and nearby (countryside) in central Sweden. The men participated in fourteen 24-h dietary telephone interviews performed over 1 y. We obtained blood samples within 2 wk after completion of the last interview. The ethical committees at the Uppsala University Hospital and the Karolinska Institutet in Stockholm approved this study.

Measurements

Data were collected on biochemical measurements of blood, anthropometric measurements, cigarette smoking status, and dietary intakes. Blood samples were drawn in the morning after

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a 12-h overnight fast. Serum was separated by centrifugation at $1200 \times g$ for 10 min at 20 °C after blood samples were held at room temperature for 2 h. Sera were stored at -70 °C until analyzed. Serum IGF-I was measured by radioimmunoassay after acid ethanol extraction (22). The sensitivity of the assay was 2 $\mu\text{g/L}$ and the within- and between-assay CVs for IGF-I were 4% and 11%, respectively. Insulin-like growth factor binding protein (IGFBP)-1 was determined by radioimmunoassay according to the method of Povoia et al (23). The antibodies used were raised in rabbits against purified human amniotic protein, and the cross-reaction with IGFBP-2 and IGFBP-3 was $<0.1\%$. The sensitivity of the assay was 3 $\mu\text{g/L}$, and the within- and between-assay CVs for IGFBP-1 were 3% and 10%, respectively. There was no significant cross-reactivity between IGF-I, IGF-II, or other peptide hormones with IGF-I antiserum.

Body mass index (BMI) was calculated by dividing body weight (in kg) by the square of height (in m). Waist was measured with the subjects in the supine position. The abdominal sagittal circumference was recorded at the umbilical level as the height of the abdomen measured from the examination couch when lying down with the legs straight.

Dietary assessment

We used the average of fourteen 24-h dietary telephone interviews conducted over 1 y (about once per month) to estimate long-term dietary intake. The research dietician who performed the telephone interviews used a standardized 24-h diet recall technique completed with probing questions. Portion sizes were described in household measures. An administrative program had been choosing random days for consecutive dietary interviews for each participant, covering all weekdays as well as weekends. The interviews were entered by using a personal computer nutrient software package MATS (24). Intakes of nutrients were calculated by using the Swedish Food Administration Food Database (25), which includes 1593 foods and dishes. For dishes reported but not included in this database, the dietician obtained recipes from the participants and entered appropriate amounts of the component foods.

Statistical analyses

We first calculated the means (\pm SDs) and proportions of covariates for this sample of men. Spearman correlation coefficients were calculated between age and other nondietary variables and IGF-I. Because the distribution of serum IGFBP-1 concentrations was positively skewed, we conducted a logarithmic transformation of this variable to improve normality.

The dietary factors considered in the present analysis were intakes of total energy, alcohol, macronutrients, vitamins (including vitamins A, B-6, C, D, and E; thiamine; riboflavin; and folate) minerals (including calcium, magnesium, potassium, and zinc), and foods rich in protein and minerals (including red meat, fish and seafood, poultry, and total milk). All intakes of nutrients except alcohol intake were energy adjusted by using the residual method (26). Each dietary variable (except poultry because of limited range of consumption) was treated as categorical (by quintiles) and continuous. We used generalized linear regression models to estimate mean IGF-I concentrations by quintiles of each dietary variable. Regression models were used to determine the differences in IGF-I concentrations that corresponded to 2-SD differences in dietary intake. All analyses were controlled

TABLE 1
Characteristics of the study population¹

Characteristic	Value
Age (y)	60.5 \pm 10.1 ²
BMI (kg/m ²)	26.3 \pm 3.2
IGF-I ($\mu\text{g/L}$)	147.5 \pm 40.9
IGFBP-1 ($\mu\text{g/L}$) ³	26 (3–93) ⁴
Current smoker (%)	21
Dietary intake ⁵	
Total energy (kcal/d)	2092 \pm 451
Alcohol (g/d)	11.6 \pm 11.8
Total fat (g/d)	79.2 \pm 9.5
Carbohydrate (g/d)	249 \pm 28
Protein (g/d)	75.7 \pm 8.6
Calcium (mg/d)	976 \pm 233
Magnesium (mg/d)	328 \pm 40
Potassium (mg/d)	3201 \pm 461
Zinc (mg/d)	10.4 \pm 1.3

¹ $n = 226$. IGF-I, insulin-like growth factor I; IGFBP-1, insulin-like growth factor binding protein 1.

² $\bar{x} \pm$ SD (all such values).

³ The distribution was positively skewed.

⁴ Median; range in parentheses.

⁵ All nutrients except alcohol were energy-adjusted by using the residual method (26).

for age (as a continuous variable). Adjustment for anthropometric variables (including weight, height, BMI, sagittal measure, and waist), smoking, and serum IGFBP-1 concentrations did not change the results; therefore, these variables were not included in the final models. We used the SAS software (version 8.2; SAS Institute Inc, Cary, NC) for analyses. All P values were two-sided; $P < 0.05$ was considered statistically significant.

RESULTS

For the 226 men included in this analysis, the mean age was 60.5 ± 10.1 y and the mean serum IGF-I concentration was 147.5 ± 40.9 $\mu\text{g/L}$ (Table 1). Their reported energy intake was 2092 ± 451 kcal/d. Age [Spearman correlation coefficient (r) = -0.44 , $P < 0.0001$] and serum IGFBP-1 (r = -0.31 , $P < 0.0001$) were inversely correlated with serum IGF-I concentrations. None of the anthropometric variables examined, including height, weight, BMI, waist, and sagittal measure, was significantly correlated with IGF-I concentrations (data not shown).

The associations between intakes of energy, alcohol, macronutrients, and micronutrients and serum IGF-I concentrations are shown in Table 2. In the age-adjusted regression analysis, protein intake was positively associated with IGF-I concentrations ($\beta = 16.0$ for 2-SD difference, P for trend = 0.001). Serum IGF-I concentrations were $\approx 17\%$ higher in men in the top quintile of protein intake than in men in the bottom quintile (P for difference between extreme quintiles = 0.005). We observed a positive association between potassium ($\beta = 11.0$ for 2-SD difference, P for trend = 0.03) and zinc ($\beta = 15.3$ for 2-SD difference, P for trend = 0.002) and serum IGF-I. However, potassium and zinc were correlated (Spearman correlation coefficient $r = 0.41$, $P < 0.0001$), and, when both nutrients were included in the same model, only zinc intake remained significantly related to IGF-I. Men in the highest quintile of zinc intake had $\approx 16\%$ higher serum IGF-I concentrations than men in the lowest quintile (P for

TABLE 2

Age-adjusted mean serum insulin-like growth factor I (IGF-I) concentrations ($\mu\text{g/L}$) with 95% CIs by quintiles of total energy, alcohol, macronutrient, and mineral intakes and the differences in serum IGF-I concentrations for 2-SD differences in the dietary variable¹

	Quintile of dietary intake					2-SD difference in intake	
	1 (Low)	2	3	4	5 (High)	β (95% CI) ²	P for β^3
Total energy (kcal/d)	<1713 [45]	1713–1955 [46]	1956–2196 [44]	2197–2412 [45]	\geq 2413 [46]		
IGF-I	147 (136, 158) ⁴	145 (134, 156)	154 (143, 165)	143 (131, 154)	149 (138, 160)	-0.1 (-10.2, 9.9)	0.98
Alcohol (g/d)	<1.8 [45]	1.8–5.0 [46]	5.1–11.9 [44]	12.0–19.9 [45]	\geq 20.0 [46]		
IGF-I	147 (136, 158)	145 (134, 156)	151 (139, 162)	149 (138, 160)	146 (135, 157)	-1.9 (-7.0, 3.2)	0.47
Total fat (g/d)	<72.3 [45]	72.3–76.8 [45]	76.9–81.6 [45]	81.7–87.0 [45]	\geq 87.1 [46]		
IGF-I	149 (138, 160)	153 (142, 164)	145 (134, 156)	141 (130, 152)	149 (138, 159)	-2.7 (-12.5, 7.1)	0.59
Carbohydrate (g/d)	<228 [46]	228–243 [44]	244–254 [45]	255–269 [45]	\geq 270 [46]		
IGF-I	148 (137, 159)	148 (137, 159)	141 (130, 152)	149 (138, 160)	150 (139, 161)	0.8 (-9.3, 10.9)	0.88
Protein (g/d)	<68.6 [46]	68.6–73.7 [43]	73.4–77.7 [46]	77.8–83.0 [47]	\geq 83.1 [44]		
IGF-I	139 (129, 150)	145 (134, 156)	141 (130, 152)	151 (140, 161)	162 (151, 173)	16.0 (6.5, 25.5)	0.001
Calcium (mg/d)	<772 [45]	772–901 [46]	901–1026 [44]	1027–1151 [46]	\geq 1152 [45]		
IGF-I	153 (142, 164)	148 (137, 159)	144 (133, 155)	139 (128, 150)	153 (142, 164)	5.2 (-4.7, 15.0)	0.30
Magnesium (mg/d)	<297 [45]	297–314 [45]	315–334 [45]	335–358 [46]	\geq 359 [45]		
IGF-I	145 (134, 156)	140 (129, 151)	154 (143, 165)	147 (136, 158)	151 (140, 162)	6.4 (-3.3, 16.2)	0.19
Potassium (mg/d)	<2832 [46]	2832–3051 [45]	3052–3303 [46]	3301–3569 [44]	\geq 3570 [45]		
IGF-I	145 (134, 156)	147 (136, 158)	141 (130, 152)	147 (136, 158)	158 (147, 169)	11.0 (1.3, 20.6)	0.03
Zinc (mg/d)	<9.3 [46]	9.3–9.9 [41]	10.0–10.6 [49]	10.7–11.5 [42]	\geq 11.6 [48]		
IGF-I	143 (132, 153)	140 (129, 151)	141 (131, 151)	147 (136, 158)	166 (155, 176)	15.3 (5.5, 25.0)	0.002

¹ All nutrients except alcohol were energy-adjusted by using the residual method (26). n in brackets.

² Regression coefficients (95% CI) from linear regression models adjusted for age.

³ P value for trend based on the continuous measure of the dietary variables.

⁴ Mean; 95% CI in parentheses (all such values).

difference between extreme quintiles = 0.002). Intakes of total energy, alcohol, total fat, and carbohydrate were not associated with IGF-I concentrations (Table 2). Also, no association was observed between intake of any of the 8 examined vitamins and IGF-I concentrations (data not shown).

We also examined the principal sources of protein and minerals, including red meat, fish and seafood, poultry, and total milk, in relation to IGF-I concentrations (Table 3). Consumption of red meat ($\beta = 6.2$ for 2-SD difference, P for trend = 0.05) and fish and seafood ($\beta = 5.8$ for 2-SD difference, P for trend = 0.07) was positively associated with IGF-I concentrations, although only the association with red meat was statistically significant. Serum IGF-I concentrations were \approx 13% higher in the highest

quintile than in the lowest quintile of red meat consumption (P for difference between extreme quintiles = 0.03). The results did not change when we included red meat, fish and seafood, poultry, and milk simultaneously in 1 model (data not shown).

DISCUSSION

In this population-based study of healthy well-nourished men, we observed that protein and zinc were significant determinants of serum IGF-I concentrations. In addition, consumption of red meat and fish and seafood, which are high in protein and minerals, was modestly positively associated with IGF-I. We examined many dietary factors; therefore, some observed associations

TABLE 3

Age-adjusted mean serum insulin-like growth factor I (IGF-I) concentrations ($\mu\text{g/L}$) with 95% CIs by quintiles of red meat, fish and seafood, poultry, and total milk intakes and differences in serum IGF-I concentrations for 2-SD differences in the food item¹

	Quintile of dietary intake					2-SD difference in intake	
	1 (Low)	2	3	4	5 (High)	β (95% CI) ²	P for β^3
Red meat (g/d)	<22.6 [45]	22.6–40.0 [45]	40.1–50.9 [44]	51.0–68.5 [46]	\geq 68.6 [46]		
IGF-I	143 (136, 150) ⁴	149 (134, 163)	156 (141, 171)	145 (132, 158)	161 (147, 175)	6.2 (-0.1, 12.5)	0.05
Fish and seafood (g/d)	<3.8 [45]	3.8–16.5 [45]	16.6–23.3 [45]	23.4–33.9 [4]	\geq 34.0 [46]		
IGF-I	156 (142, 170)	129 (116, 143)	146 (133, 160)	141 (127, 155)	165 (152, 179)	5.8 (-0.5, 12.1)	0.07
Poultry (g/d)	0 [183]	\geq 0.1 [43]					
IGF-I	149 (142, 156)	141 (127, 156)				-3.0 (-9.3, 3.4)	0.36
Total milk (g/d)	0 [78]	0.1–27.8 [13]	27.9–132.2 [45]	132.3–248.0 [45]	\geq 248.1 [45]		
IGF-I	149 (138, 149)	134 (106, 162)	157 (143, 171)	150 (136, 164)	138 (124, 152)	-1.7 (-8.2, 4.8)	0.61

¹ 2 SDs for each food item were as follows: red meat, 31.2 g/d; fish, 17.0 g/d; poultry, 5.5 g/d; and total milk, 136 g/d. n in brackets.

² Regression coefficients (95% CI) from linear regression models adjusted for age.

³ P value for trend based on continuous measure of the food item.

⁴ Mean; 95% CI in parentheses (all such values).

may be due to chance. However, our findings are consistent with those of previous studies. Our results are most directly generalizable to well-nourished middle-aged and elderly men.


Studies in animals and children have shown that restricted intakes of energy, protein, and zinc are associated with lower concentrations of IGF-I (9–11, 27–29). A positive association between zinc intake and IGF-I concentrations was also observed in a study of postmenopausal women (30). Likewise, recent analyses of a subgroup of men from the Health Professionals Follow-Up Study (14) and a subgroup of women from the Nurses' Health Study (13) indicated a positive association between zinc intake and IGF-I concentrations. Those 2 studies further reported that individuals with a high protein intake had higher IGF-I concentrations than those with a low protein intake. A positive association between intake of protein and IGF-I has been reported also in other studies (17, 18), although not in all (19, 20). These inconsistencies may reflect different ranges of protein intakes studied, different characteristics of study populations, and validity of measurement of protein intake. In the present study, we reduced random within-person variation by using the average dietary intakes of fourteen 24-h dietary interviews. This should improve validity compared with previous studies in which dietary intakes were assessed only at one occasion with a dietary questionnaire.

Our findings that show a significant positive association between red meat consumption and IGF-I concentrations are consistent with results of some (12, 16), but not all (13–15), previous cross-sectional studies. Furthermore, we observed that men with a high consumption of fish and shellfish had higher IGF-I concentrations than men with low consumption. Although our results for fish did not achieve statistical significance (possibly owing to a relatively small sample size), they are in accord with previous studies in men (14) and women (13).

An increasing body of evidence indicates that a high consumption of red meat may increase the risk of prostate (31) and colorectal cancers (32). In addition, high IGF-I concentrations have been associated with increased risk of these 2 cancers (1), thus raising the possibility that diet may affect cancer risk by modulation of the IGF-system. There is some evidence that IGF-I may predict the risk of advanced-stage prostate cancer only (33) and not of earlier stages (33, 34). In the present study, the concentration of serum IGF-I in men with high consumption of red meat is of the same order of magnitude as reported by other studies in which an association between high serum IGF-I and prostate cancer risk was reported (35).

Several strengths and potential limitations of our study merit comment. The main strengths include its population-based design and the detailed dietary data. The average intake of fourteen 24-h dietary interviews performed over 1 y was used to assess long-term dietary intake. This accurate dietary assessment method would account for dietary changes over time and minimize random error in the measurement of diet. This study was limited by its cross-sectional nature; therefore, we cannot determine the temporal association between changes in dietary intake and IGF-I concentrations. Another limitation is the lack of measurement of free-circulating IGF-I, which may better reflect IGF-I bioactivity than total IGF-I (36). We also did not have data on IGFBP-3, which may regulate IGF-I bioactivity.

In conclusion, in this population-based study, we observed positive associations between intakes of protein, zinc, red meat,

and fish and IGF-I concentrations. In view of the potential clinical and public health importance of these findings, the association between dietary intake and IGF-I concentrations in well-nourished free-living adults deserves further study. 

SCL, KW, KB, and AW contributed to the study concept and design, interpreted the results, and critically reviewed the manuscript. SCL conducted the statistical analyses and wrote the manuscript. All authors reviewed the final version of the manuscript. None of the authors had any conflicts of financial or personal interest.

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