Nutritional Predictors of Insulin-like Growth Factor I and Their Relationships to Cancer in Men[1]

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Abstract

The insulin-like growth factor (IGF) axis may play opposing roles in health and disease. The age-related declines in growth hormone and IGF-I may be associated with potentially deleterious changes in body composition and functioning, but recent studies suggest that IGF-I levels may be related to risk of prostate, colorectal, premenopausal breast, and possibly other cancers. Thus, we studied dietary influences on plasma IGF-I and IGF-I:IGF-binding protein-3 ratio in 753 men in the Health Professionals Follow-Up Study who completed a food frequency questionnaire. In this generally well-nourished population of middle-aged to elderly men, plasma IGF-I and IGF-I:IGF-binding protein-3 molar ratio tended to increase with higher intake of protein and minerals, including potassium, zinc, magnesium, calcium, and phosphorus. Men with relatively high intakes of total protein (top quintile) and minerals (top quintile of the five minerals combined) had a 25% higher mean plasma level of IGF-I compared with those in the low quintiles simultaneously. The major sources of animal protein, including milk, fish, and poultry, but not red meat, as well as total vegetable protein, were associated with an increase in IGF-I levels. Energy intake was positively related to plasma IGF-I level but only in men with body mass index <25 kg/m^2. The age-related decline in plasma IGF-I may be exacerbated by low intakes of protein and minerals. The potential role of these dietary factors on cancer risk through altering IGF-I levels requires study.

Introduction

The IGF[3] axis plays a critical role in health and disease. As adults age, GH secretion declines, leading to a decrease in circulating IGF-I (1). The declines in GH and IGF-I may be associated with reduced lean body mass, increased body fat, reduced muscle power and exercise tolerance, and decreased bone mass (2). Yet many older individuals maintain youthful levels of GH and IGF-I. Whereas there may be physiological and health benefits to averting GH and IGF-I deficiencies in older ages, recent studies suggest that higher IGF-I bioactivity may be related to an increased risk of several cancer types, including prostate (3, 4), colorectal (5), and premenopausal breast cancers (6). Given the potential opposing roles of the IGF-I axis on overall health, additional study is necessary to better understand the determinants of IGF-I bioactivity in a generally healthy population.

Nutritional factors are critical regulators of IGFs (7). In particular, undernutrition of either protein or energy intake substantially lowers IGF-I levels (7). For example, fasting for 10 days causes a 4-fold reduction in IGF-I to levels associated with GH deficiency (8). Fasting humans have increased GH levels, but GH resistance in the liver occurs, and IGF-I secretion is reduced (9, 10). Overconsumption may increase IGF-I somewhat, but excess calories are not nearly as strong a stimulus as nutritional restriction (7). Short-term feeding studies of protein deprivation demonstrate a potent and independent role of protein on IGF-I levels. Deficiency of essential amino acids, in particular, has a severe depressing effect on IGF-I levels (11). A high carbohydrate diet also increases IGF-I levels relative to a high fat diet, possibly by maintaining hepatic sensitivity to GH (7).

In addition to total energy and protein intake, potassium, magnesium, and zinc may also influence IGF-I levels (12), but this evidence is largely from animal experiments and studies of seriously malnourished children (13–16), and their role in adults is largely unstudied. In addition, because the best dietary sources of these minerals are also good sources of essential amino acids, the independent influence of minerals remains unresolved. Limited data suggest that milk may increase IGF-I levels (17), but whether the increase is from the essential amino acids and minerals in milk or from other factors such as bovine IGF-I is unknown.

A recent analysis of women in the Nurses' Health Study found that higher energy, protein, and milk intakes were associated with higher levels of IGF-I (18). Here, we examined the cross-sectional associations between dietary factors and plasma levels of IGF-I, IGFBP-3, the major circulating binding protein of IGF-I, and the IGF-I:IGFBP-3 molar ratio in a population of middle-age to elderly male health professionals.

Received 5/2/02; revised 10/9/02; accepted 11/25/02.
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[1] Supported by U.S. Department of Defense Grant DAMD17-98-1-8491 and NIH Grants CA72036 and CA55075.
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[3] The abbreviations used are: IGF, insulin-like growth factor; GH, growth hormone; IGFBP-3, IGF-binding protein-3; HPFS, Health Professionals Follow-up Study; BMI, body mass index.

Materials and Methods

The Study Population. The HPFS cohort is an ongoing prospective study of 51,529 United States male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, 40 to 75 years of age, in 1986 (19). Through the baseline mailed questionnaire in 1986, respondents provided information on age, marital status, height and weight, ancestry, medications, smoking history, disease history, physical activity, and diet. Questionnaires are sent to surviving men every 2 years to update exposures and medical history.

The Semiquantitative Food Frequency Questionnaire. We used a semiquantitative food frequency questionnaire to assess dietary factors. This questionnaire, described in detail previously (20), was first administered in 1986, and subsequently in 1990 and 1994. The questionnaire contained a list of 131 food and beverage items. For each item listed, a commonly consumed unit or portion size was specified. The men were asked how often, on average, over the past year, they ate that amount of each food. Participants chose from among nine possible responses for frequencies, which ranged from never to six or more times per day. We also queried about the brand of breakfast cereal, the brand, duration, and frequency of multivitamin and individual vitamin and mineral supplement use, and the types of fat commonly used. The dietary questionnaire also included an open-ended section for unlisted foods. We computed nutrient intakes by multiplying the consumption frequency of each unit of food by the nutrient content of the specified portions, using composition values from United States Department of Agriculture sources (21) supplemented with other data.

In 1986, we evaluated the validity of nutrient and food consumption measured by the questionnaire among a sample of 127 cohort members from the Boston area (20, 22). The mean correlation coefficients between intakes determined by two 1-week diet records and the dietary questionnaire (adjusting for week-to-week variation in the diet records) were 0.65 for nutrients and 0.63 for specific foods.

Collection of Blood Specimens. In 1993 and 1994, 18,018 men in the HPFS provided blood samples. For collection, the participants received a kit containing all of the necessary supplies to have a blood sample drawn, including three 10-ml tubes with EDTA. The kits were returned through overnight mail while chilled by ice. On receipt at our laboratory, samples were kept chilled until centrifugation, and then separated into plasma, buffy coat, and RBCs. The processing was usually complete within several hours of receipt of the specimens so that the vast majority of samples were frozen within 29 h of venipuncture. Specimens in cryotubes were stored in liquid nitrogen freezers from −196°C to −130°C.

Laboratory Assays. Plasma levels of IGF-I and IGFBP-3 were analyzed by ELISA with reagents from Diagnostic Systems Laboratory (Webster, TX) in the laboratory of Dr. Michael Pollak (McGill University, Montreal, Quebec, Canada). The mean intra-assay coefficients of variation for IGF-1 and IGFBP-3 from blinded control samples in various runs were generally well under 5%. In a sample of 140 men of this cohort, plasma IGF-I and IGFBP-3 assessed 3 years apart and assayed together from the same individuals yield good correlations (r = 0.70 for IGF-I and r = 0.68 for IGFBP-3). Circulating IGF-I is bound mainly to IGFBP-3, and the molar ratio of IGF-I to IGFBP-3 may be a marker of bioactive IGF-I and a risk factor for cancer. We calculated the IGF-I:IGFBP-3 ratio as an indicator of bioactive IGF-I using the following equivalents for conversion: 1 ng/ml IGF-I = 0.130 nm IGF-I, and 1 ng/ml IGFBP-3 = 0.036 nm IGFBP-3.

Data Analysis. IGF-I Predictor Analyses. The population for this analysis came from three sets of samples analyzed for plasma IGF-I and IGFBP-3 from the pool of 18,018 HPFS archived blood samples. These were controls from a nested case-control study of benign prostatic hyperplasia, controls from a nested case-control study of prostate cancer (done in two phases, for cases up to 1996, and for additional cases to 1998), and from a sample of Caucasian, African-American, and Asian-American men from the HPFS used to study racial differences (23). None of the men had a diagnosis of cancer at the time of blood draw.

We examined the relationship between dietary factors assessed by the 1994 food frequency questionnaire, and plasma levels of IGF-I, IGFBP-3, and the IGF-I:IGFBP-3 molar ratio from blood collected approximately at the same time using linear regression. We considered: (*a*) total energy intake, including energy intake excluding that from alcohol; (*b*) intake of macronutrients, including animal and vegetable protein separately; (*c*) intake of various minerals; (*d*) intakes of vitamins; and (*e*) specific food sources of these nutrients. The nutrients were adjusted for total energy intake using residual analysis. Because previous evidence suggests that more than one mineral, or their overall balance, may be important, and many of the minerals are intercorrelated, as they have common dietary sources, we first examined overall mineral intake. Specifically, we added the quintile score (1–5) of each of potassium, zinc, magnesium, calcium, and phosphorus to form a score ranging from 5 to 25. This score was then divided into quintiles. We also used linear regression to examine the independent effects of each of the minerals, which tend to be correlated with each other. Indicator terms for laboratory run were included in all of the models, because the samples were analyzed at four separate times, albeit in the same laboratory using the same assays. Fasting status was not included in the final models, because this was not related to IGF-I or IGFBP-3 levels, and inclusion of fasting status into the model did not alter the results.

Results

We had complete information for dietary and covariate data, and plasma IGF-I and IGFBP-3 data for 753 men. The average age at the time the blood was drawn was 65 years (SD ± 8.0), and the range was from 46 to 81 years of age. Of these men, 83.1% were self-described as Caucasian, 5.6% as African-American, 6.9% as Asian-American, and 4.5% as other race/ethnicity. Non-Caucasian men were over-sampled from the cohort to participate in this substudy. Only 3.6% of the men were current smokers in 1994.

We first examined total energy intake and macronutrients in relation to plasma IGF-I, IGFBP-3, and the IGF-I:IGFBP-3 molar ratio. As shown in Table 1, no associations were noted for intakes of total energy (excluding energy intake from alcohol sources). The results were not appreciably different for total energy including alcohol. The mean levels of IGF-I by BMI level were <23 kg/m^2:180 ng/ml; 23–24.9:187; 25–27.5:180; 27.6–29.9:181; and >30:179. We stratified men by BMI level, and found that in men with low BMI, total energy had a modest positive association with total IGF-I.

Table 2 shows no association between IGF-I, IGFBP-3, or their ratio with energy-adjusted fat intake. A slight positive association was suggested between total carbohydrate intake and plasma IGF-I and IGF-I:IGFBP-3. Total protein intake was positively associated with plasma IGF-I, IGFBP-3, and IGF-I:

Table 1 Mean plasma levels of IGF-1, IGFBP-3, and IGF-1:IGFBP-3 molar ratio by intakes of energy (quintiles) in 753 male health professionals

Calories[a] median daily intake	(*n*)	IGF-1 (ng/mL)	IGFBP-3 (ng/mL)	IGF-1:IGFBP-3 (molar ratio)
Total Population				
1226	161	182	3150	0.226
1536	134	181	3117	0.227
1860	142	181	3078	0.228
2173	158	184	3080	0.234
2784	158	189	3194	0.231
P (trend)		(0.22)	(0.45)	(0.29)
BMI <25 kg/m^2				
1251	71	180	3173	0.222
1536	59	177	2977	0.233
1834	54	185	3155	0.230
2192	72	190	3193	0.234
2762	62	196	3268	0.231
P (trend)		(0.03)	(0.12)	(0.27)
BMI ≥25 kg/m^2				
1207	90	185	3145	0.229
1536	75	182	3174	0.224
1874	88	177	2996	0.228
2139	86	178	2968	0.234
2784	96	185	3129	0.232
P (trend)		(0.94)	(0.80)	(0.62)

[a] Calories exclude those from alcohol intake. All results are adjusted for age and laboratory run.

Table 2 Mean plasma levels of IGF-1, IGFBP-3, and IGF-1:IGFBP-3 molar ratio by intake of nutrients in quintiles in male health professionals

Nutrient[a]	Median daily intake	IGF-1 (ng/mL)	IGFBP-3 (ng/mL)	IGF-1:IGFBP-3 (molar ratio)
Total Fat (g)				
	47.8	188	3129	0.234
	58.4	184	3218	0.225
	66.7	181	3069	0.230
	74.0	186	3129	0.232
	84.0	179	3058	0.227
	P (trend)	(0.16)	(0.24)	(0.54)
Carbohydrate (g)				
	192.6	181	3209	0.220
	232.8	184	3087	0.233
	254.8	179	3113	0.226
	277.9	185	3058	0.236
	310.0	189	3168	0.232
	P (trend)	(0.13)	(0.97)	(0.04)
Protein (g)				
	69.1	173	3082	0.220
	79.5	177	3043	0.227
	85.9	182	3081	0.230
	93.8	187	3178	0.230
	107.1	201	3257	0.242
	P (trend)	(<0.0001)	(0.01)	(<0.0001)
Animal protein (g)				
	39.2	168	3042	0.217
	51.3	181	3113	0.226
	59.1	181	3032	0.233
	67.2	190	3190	0.231
	81.7	200	3273	0.241
	P (trend)	(<0.0001)	(0.01)	(<0.0001)
Vegetable protein (g)				
	20.2	173	3114	0.217
	23.9	183	3086	0.230
	27.0	179	3100	0.228
	30.0	191	3224	0.231
	36.0	194	3126	0.242
	P (trend)	(<0.0002)	(0.59)	(<0.0001)

[a] Protein, carbohydrate, and fat are adjusted for total energy. All results are adjusted for age and laboratory run. Animal and vegetable protein intakes are adjusted for each other.

IGFBP-3. Comparing the means of the top *versus* the low quintile of protein intake, the difference was ~15% for IGF-I and 10% for IGF-I:IGFBP-3. An association was observed both for animal protein and vegetable protein. Fig. 1 shows the joint effect of animal and vegetable protein on plasma IGF-I level; as shown, plasma IGF-I level rises across both increasing intake of animal and vegetable protein.

We next examined the intake of minerals in relation to plasma IGF-I, IGFBP-3, and their ratio. As shown in Table 3, overall mineral intake was associated positively with plasma IGF-I, IGFBP-3, and IGF-I:IGFBP-3. Comparing the top *versus* the low quintile, the difference was ~15% for IGF-I and 10% for IGF-I:IGFBP-3. Because dietary sources of protein and minerals may overlap (*e.g.*, meat, dairy), we examined protein and minerals in the same model. Although the results were somewhat attenuated, each remained highly significantly related to plasma IGF-I, IGFBP-3, and IGF-I:IGFBP-3. For example, in the unadjusted model, the difference in mean IGF-I between high and low quintiles of protein was 28 ng/ml in the unadjusted model and 18 ng/ml when adjusted for mineral intake. For mineral intake, the difference was 32 ng/ml in the unadjusted model and 25 ng/ml when adjusted for protein intake. There was an ~25% difference in mean IGF-I between those in the top quartiles both of protein and mineral intakes compared with those in the bottom quartiles of both.

To examine whether some of the individual minerals were more important than the others, we simultaneously modeled potassium, zinc, magnesium, calcium, and phosphorus in relation to plasma IGF-I, IGFBP-3, and IGF-I:IGFBP-3. The correlation coefficients between individual minerals were as follows: calcium and zinc, $r = 0.35$; calcium and potassium, $r = 0.32$; calcium and magnesium, $r = 0.43$; calcium and phosphorus, $r = 0.61$; zinc and potassium, $r = 0.11$; zinc and magnesium, $r = 0.31$; zinc and potassium, $r = 0.18$; potassium and magnesium, $r = 0.64$; potassium and phosphorus, $r = 0.47$; and magnesium and phosphorus, $r = 0.61$. The strongest independent (positive) associations for IGF-I were with phosphorus intake, with *P*s of <0.0001, 0.015, and 0.004 for plasma IGF-I, IGFBP-3, and IGF-I:IGFBP-3, respectively. With all of the minerals in the model, the only other statistically significant association was between zinc intake and IGF-I:IGFBP-3 ($P = 0.04$). Of note, phosphorus tends to be correlated both with the other minerals and with protein, as both meat and dairy products are the primary sources of phosphorus. When protein was added to the model with the individual minerals, the confidence intervals for specific minerals tended to widen, and results were generally not statistically significant. Zinc from supplements, less correlated with overall protein and mineral intake, was related to higher levels of IGF-I ($P = 0.04$) and IGF-I:IGFBP-3 ($P = 0.006$) controlling for protein and total minerals.

We next examined the major food sources of protein and minerals, which included fish, red meat, poultry, and total milk. The mean intake was 0.60 servings/day for red meat, 0.38 for fish, 0.37 for poultry, and 0.87 for milk. When adjusted for each other, fish and milk were associated with higher IGF-I and IGFBP-3, but not with a higher ratio (Table 4). Only poultry intake was associated with a higher IGF-I:IGFBP-3 ratio. When adjusted for total protein and mineral intake, the association between IGF-I and IGFBP-3 with fish remained but that with milk did not persist. Inclusion of either minerals or protein

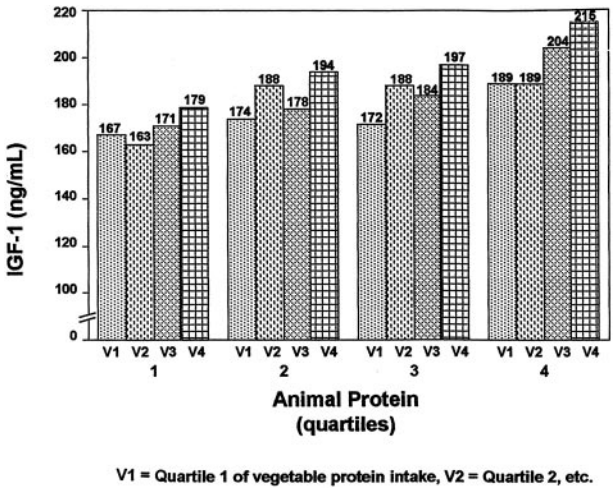

Fig. 1. Mean plasma IGF-I (ng/ml) by intakes of animal and vegetable protein.

individually in models caused milk to lose statistical significance. With protein in the model, the *P* for milk was 0.15, and with minerals in the model, the *P* was 0.94. Red meat (beef, pork, or lamb as a main dish) was not associated with IGF-I level.

As expected, plasma IGF-I, IGFBP-3, and their ratio decreased with increasing age. On the basis of the linear regression model, plasma IGF-I decreased by 2.4 ng/ml for each increment of 1 year. Thus, over a 20-year period, an ~48 ng/ml average decrement in plasma IGF-I is expected. Fig. 2 illustrates three strata of age jointly with plasma IGF-I levels (medians and interquartile ranges). As expected, the lowest ranges were observed for the oldest men with the lowest intakes of protein and minerals. Of note, older men (mean age = 74 years) with high protein and mineral intakes had median plasma IGF-I levels comparable with younger men (mean age = 55 years) who had relatively low protein and mineral levels using the same cutpoints.

With total protein and minerals in the model, water-soluble vitamins (vitamin C, thiamine, folate, B6, B2, and B12) either as a group or individually were not related to IGF-I, IGFBP-3, or IGF-I:IGFBP-3. Among fat-soluble vitamins (vitamins A, D, and E), only vitamin E was associated with an increased molar ratio (*P* for trend = 0.02) in a multivariate model with protein, minerals, and other vitamins.

Table 3 Age-adjusted mean plasma levels of IGF-1, IGFBP-3, and IGF-1:IGFBP-3 molar ratio by intake of minerals in male health professionals

	Quintile[a]	IGF-1 (ng/mL)	IGFBP-3 (ng/mL)	IGF-1/IGFBP-3 (molar ratio)
Minerals				
	1 (low)	169	2979	0.223
	2	175	3096	0.221
	3	186	3217	0.225
	4	189	3132	0.236
	5 (high)	201	3211	0.244
	P (trend)	(<0.001)	(0.009)	(<0.001)

[a] Quintiles based on adding quintile (1–5) of each of potassium, magnesium, zinc, calcium, and phosphorus, and dividing the total score into quintiles. Results are adjusted for age and laboratory run.

Discussion

We observed that even in a generally well-nourished population of middle-aged to elderly men, greater intakes of protein and minerals are associated with higher plasma IGF-I and IGF-I:IGFBP-3 ratio, and the age-related decline in GH and IGF-I may be exacerbated by low intakes of protein and minerals. From the literature based mostly on short-term feeding studies examining extreme ranges of intakes, we had hypothesized that three nutritional factors, energy balance, and intakes of protein and minerals, could be important determinants of IGF-I in a free-living population.

We did not find an appreciable association with total energy intake. In studies of energy restriction, IGF-I levels lower dramatically within weeks, whereas in situations of acute energy excess, the level of IGF-I is more stable, although it may increase slightly (7). Our weak results for total energy are not surprising, because energy restriction is not prevalent in this population, and because our questionnaire is not designed to specifically assess energy intake with great precision. We did find a modest positive association between energy intake and IGF-I level among leaner men but not among men with higher BMI. In a recent analysis of the Nurses' Health Study, total energy intake was also shown to be related to increasing IGF-I levels among women with BMI <25 kg/m^2 (P for linear trend = 0.0007) but not in women with BMI ≥ 25 kg/m^2 (P = 0.75; Ref. 18). Interestingly, levels of IGF-I in obese individuals may be relatively resistant to the effects of energy restriction as long as protein intake is adequate, possibly because obese individuals are able to use their fat reserves as a source of energy, and thus maintain their IGF-I levels (7). It is also possible that energy intake is reported better in leaner individuals, thus increasing the ability to detect an association between energy and IGF-I level.

Animal studies, short-term metabolic interventions in humans, and studies of malnourished children indicate that essential amino acids and specific minerals would likely be the most important nutrient determinants of IGF-I (13–16) besides energy restriction. Our study extends these results to long-term dietary patterns in free-living, generally well-nourished adult populations with Western diets. Although most of the variability in IGF-I and IGF-I:IGFBP-3 ratio remained unexplained, a substantial 25% difference in mean IGF-I level existed between individuals with high intakes of protein and minerals relative to those with low intakes. Notably, the median protein intake for the study population for the lowest quintile was 69.1 grams/day, which is above the recommended daily intake. For the minerals, the medians of the lowest quintile were 507 mg for calcium, 1152 mg for phosphorus, 2709 mg for potassium, 290 mg for magnesium, and 9.5 mg for zinc. The average levels of IGF-I may be even lower with lower protein and mineral intakes, which may be prevalent in some elderly populations. Some data suggest that deficiencies of vitamins, particularly thiamine (13), may depress IGF-I levels, but severe vitamin deficiencies are uncommon in our study population.

Adjusting for total energy, we found that total fat had a slight but not significant inverse trend with plasma IGF-I, whereas carbohydrates had a slight positive trend, especially with the IGF-I:IGFBP-3 ratio. Similar patterns were noted in an analysis in the Nurses' Health Study (18). These results suggest that among macronutrients, the role of proteins is more important that that of carbohydrates or fat in influencing IGF-I levels.

The dietary factors most closely related to high IGF-I and IGF-I:IGFBP-3 ratios included high intake of fish, poultry, and total milk, the most important sources of essential amino acids

Table 4 Changes (Δ) in plasma IGF-1, IGFBP-3, and IGF-1:IGFBP-3 molar ratio for specified increment of item in male health professionals

Item	Serving increment		IGF-1 (ng/mL) (Δ)	IGFBP-3 (ng/mL) (Δ)	IGF-1:IGFBP-3 (molar ratio) (Δ)
Fish	3 servings/wk	Multivariate 1[a]	7.5[b]	92[b]	0.002
		Multivariate 2[a]	6.2[b]	87[b]	0.001
Poultry	3 servings/wk	Multivariate 1	1.9	−33	0.006[b]
		Multivariate 2	0.3	−38	0.005
Red meat	3 servings/wk	Multivariate 1	−1.3	−1	−0.001
		Multivariate 2	−1.5	−13	−0.001
Milk	1 serving/day	Multivariate 1	5.4[b]	64[b]	0.002
		Multivariate 2	0.5	40	−0.002

[a] Multivariate 1, adjusted for age and laboratory run and other food items (fish, poultry, red meat, milk). Multivariate 2, adjusted for age, laboratory run, protein, and minerals.
[b] $P < 0.05$.

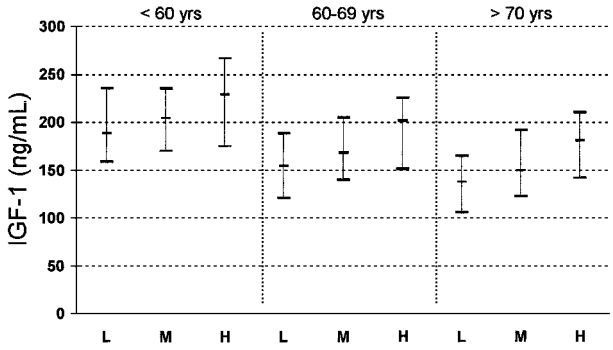

Fig. 2. Median and interquartile range of plasma IGF-I (ng/ml) by combined intake of protein and minerals (*L* = low, protein tertile 1, mineral tertile 1; *M* = medium, others; *H* = high, protein tertile 3, mineral tertile 3) by different age groups in male health professionals.

and minerals. These findings were similar to the Nurses' Health Study analysis (18), which found milk and fish but not red meat associated with higher IGF-I levels. Both animal and plant sources of protein were independently related to IGF-I, strongly indicating that protein, and not a correlate, was the actual factor. The lack of an association between red meat intake and plasma IGF-I was somewhat surprising, because red meat is an important source of protein and some minerals. Some potential contributing factors were that red meat consumption was relatively low in this health conscious population, and men consuming lower intakes of red meat tended to eat more fish and slightly less mineral intake overall. Supporting this supposition, in this population, red meat intake was only moderately correlated with total protein intake ($r = 0.18$) but inversely correlated with mineral intake ($r = -0.11$). An exploratory analysis of all of the food items in our questionnaire categorized in food groups using stepwise regression supported our results of foods high in protein and minerals being the major determinants of IGF-I levels, and indicated that it is unlikely that we missed identifying other substantial factors.

Separating specific effects of individual minerals is problematic, because these tend to come from the same sources and probably act in shared pathways. Phosphorus had the strongest association, but multivariate models suggested the reason was that phosphorus is a particularly good marker of both meat and dairy intake. Also, an association between zinc intake and IGF-I:IGFBP-3 was notable because high intakes of zinc were associated largely with supplements, allowing us to separate the effect of zinc apart from other minerals, which tended to come more from common food sources. Other evidence suggests an independent role for zinc on IGF-I levels (12, 15, 16). In the Nurses' Health Study, intake of zinc, whether from food source only or including supplements, was associated with higher levels of IGF-I (18).

Another important finding of our study is that cow milk may increase IGF-I levels, but when we controlled for protein and minerals, milk was no longer a significant factor. In a recent randomized intervention study of 204 healthy men and women 55–85 years of age, individuals who consumed three servings per day of nonfat or 1% fat milk for 12 weeks had a statistically significant 10% increase in serum IGF-I levels compared with those who consumed no milk (17). Milk contains IGF-I, regardless of treatment of the cows with recombinant bovine somatotropin for milk production, but whether intact growth factor can be absorbed with milk and increase circulating IGF-I levels is unknown (24–26). Some recent animal data indicate that some IGF-I can be absorbed intact from milk (27), but most experts do not believe that IGF-I would retain bioactivity if ingested p.o. because of rapid proteolysis in the upper gut (24, 25). Our findings from multivariate models suggest that the major influence of milk on IGF-I levels is likely related to its nutrient content, although we cannot exclude the possibility of additional increases in IGF-I induced by milk intake from recombinant bovine somatotropin-treated cows.

A potential implication of our study concerns the age-related decline in GH and IGF-I (1). Although the decrease in GH may be related in part to irreversible organic changes in the hypothalamus and pituitary axis, dietary and lifestyle factors have the potential to accentuate or ameliorate this decline. We show here that dietary protein and mineral intake has an appreciable influence. As seen in Fig. 2, in the oldest group of men with high protein and mineral intakes, the median and interquartile range of circulating IGF-I was similar to that of men 10 years younger with intermediate intakes of these, and to that of men 20 years younger with relatively low intakes. The lowest IGF-I levels were observed in the oldest men with low intakes of proteins and minerals.

Some have advocated treatment using GH replacement in aging individuals with reduced IGF-I levels (28). Whereas this approach may be appropriate for those with absent or profoundly reduced GH, there is little study of clinical benefits and adverse effects of GH replacement in those with more modest reductions in GH and IGF-I. Our results suggest that perhaps moderate declines in IGF-I in many elderly individuals might potentially be offset by optimizing diet. Short-term feeding studies show that dietary changes may improve physiological

parameters for the IGF axis. For example, increased consumption of milk led to increases in IGF-I and decreases in parathyroid hormone, which were associated with reduced bone resorption (17). Also, increases in protein consumption in elderly women with marginal protein intake increased circulating IGF-I and muscle mass relative to women who remained on marginal intakes (29). However, the long-term effects of GH replacement remain unestablished.

In summary, a diet high in protein and minerals in middle-aged to elderly men was associated with higher plasma IGF-I and IGF-I:IGFBP-3. The influence of such a diet on overall health in aging individuals, including cancer risk, requires additional study.

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Cancer Epidemiol Biomarkers Prev 2003;12:84-89.