

Effects of zinc and other nutritional factors on insulin-like growth factor I and insulin-like growth factor binding proteins in postmenopausal women¹⁻³

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ABSTRACT Insulin-like growth factor I (IGF-I) is a critical factor in the regulation of various physiologic effects, including bone formation and protein metabolism. Nutrient intake is a main regulator of circulating IGF-I. The relation of zinc status and IGF-I in adulthood has not been studied adequately even though suboptimal intakes of zinc are reported widely in the elderly. This study examined the relation between calculated nutrient intakes from 119 postmenopausal women and concentrations of IGF-I and IGF binding proteins (IGFBPs). Dietary intake was evaluated by 4-d weighed diet records at baseline and 2 y. Mean intakes of 25 nutrients were calculated. Concentrations of IGF-I and IGFBPs were measured by radioimmunoassays at baseline and 2 y. Mean age (63 ± 4 y), weight (66 ± 9 kg), and nutrient intake were correlated with the mean IGF-I concentration at baseline (172 ± 57 $\mu\text{g/L}$) and 2 y (142 ± 43 $\mu\text{g/L}$). IGF-I concentrations were significantly correlated with mean protein and zinc intake at baseline ($r = 0.313$, $P = 0.001$; $r = 0.298$, $P = 0.001$, respectively) and 2 y ($r = 0.256$, $P = 0.008$; $r = 0.331$, $P = 0.001$, respectively). After age, weight, and other nutrient intakes were adjusted for in multiple regression at baseline and 2 y, zinc remained the major determinant of IGF-I concentrations. These results suggest that low zinc intake is associated with low IGF-I concentrations in healthy postmenopausal women and that the effects of zinc may be independent of protein intake. *Am J Clin Nutr* 1998;68:200–6.

KEY WORDS Zinc, insulin-like growth factor I, IGF-I, insulin-like growth factor binding proteins, IGFBPs, protein, 4-d weighed diet records, postmenopausal women, bone

INTRODUCTION

Nutrient intake is an important regulator of insulin-like growth factor I (IGF-I) concentration and IGF-I has been used as a marker of nutritional status (1). With age, nutrient intake falls (2) because of various factors, including poor dentition, psychologic and physical barriers, illness, and lack of financial resources. The age-related reduction seen in serum IGF-I concentrations (3) and in the aging skeleton (4–6) may be explained in part by this reduction in nutrient intake and may reflect poor nutritional status of the individual. Because IGF-I is a critical factor in the regulation of bone formation, resorption, and calcium homeostasis (4), differences in bone turnover rates seen in

the elderly may be associated with individual variations in IGF-I concentrations. Thus, age-related bone loss could in part be associated with reductions in IGF-I concentrations due to reduced nutrient intake.

Restricted intakes of energy, protein, and zinc in animals (7–11) and children (12, 13) are associated with reduced concentrations of serum IGF-I and reduced growth, both of which are improved with nutritional repletion and in cases of zinc deficiency, zinc supplementation (12, 13). Recent investigation suggests that the effects of zinc deprivation on IGF-I concentrations may be independent of protein and energy intake (9, 10, 14). Reductions in energy and zinc intakes lead to reduced concentrations of serum IGF-I, growth hormone receptors, and growth hormone binding proteins (8, 11, 14). The mechanism responsible for reduced serum IGF-I in zinc deficiency is associated with decreased hepatic IGF-I gene expression and defects in the intracellular growth hormone–signaling pathway that are restored by supplemental zinc (8, 9, 14). Zinc deficiency per se affects the stability of the 7.5-kilobase IGF-I mRNA transcript and may affect the abundance, binding affinity, and stability of the protein (8, 15). The majority of circulating IGF-I (75–80%) is bound to the most abundant serum IGF binding protein, IGFBP-3. In states of protein deficiency, the preferential binding of IGF-I to the 150-kD circulating complex composed of IGFBP-3 and an acid-labile subunit is reduced and IGF-I subsequently binds to smaller-molecular-weight IGFBPs. These smaller proteins can pass through capillaries, leading to reduced circulating concentrations of IGF-I (15). This suggests that protein and zinc deficiency may also play a role in the stability of the IGFBPs and the clearance of IGF-I from the serum.

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The relation of zinc status and serum IGF-I in adulthood has not been adequately studied even though suboptimal intakes of zinc are reported widely in this study and studies of other elderly populations (2, 16–18). Poor wound healing, dermatitis, and depressed immune response are commonly seen in aging individuals and are associated with reduced zinc status (19). Studies in osteoporotic women have shown increased urinary excretion of zinc compared with age-matched control subjects (20). Hyperzincuria may reflect the increased bone resorption that is associated with aging. Further evidence suggests that bone zinc is lost in times of calcium deficiency (21), which is pronounced in aging women as calcium requirements increase beyond usual dietary intakes. It seems likely that the increased rates of bone turnover seen in postmenopausal women along with reduced nutrient intake will negatively affect zinc intake and excretion. Concentrations of serum IGF-I may therefore be affected.

The aim of this study was to determine whether nutrient intakes assessed from 4-d weighed diet records were associated with concentrations of IGF-I and serum IGF-BPs in a group of healthy community-dwelling postmenopausal women. We measured three IGF-BPs in this study. IGF-BP-3 was measured because it is the predominant IGF-BP in serum. IGF-BP-4 and IGF-BP-5 were measured because of recent *in vitro* and *in vivo* studies that emphasize an important role for these two binding proteins in modulating IGF actions in bone (22–24).

SUBJECTS AND METHODS

Subjects

The dietary intake and biochemical data of 129 female subjects entered into a clinical trial to assess the effects of calcium and exercise on bone density (25) were evaluated. One hundred twenty-nine subjects had IGF-I, IGF-BP-4, and IGF-BP-5 concentrations measured at baseline and 2 y. Only 47 samples were available for analysis of IGF-BP-3. Each subject's weight (kg) and stature (cm) was measured.

The four interventions that were studied for 2 y were as follows: placebo; a calcium lactate gluconate tablet (1 g/night, Sandoz; Sandoz, Basel, Switzerland); milk powder containing 1 g Ca; and a calcium tablet (1 g/night) and exercise (25). Women were eligible for the study if they were between 50 and 70 y of age and were ≥ 10 y postmenopausal. All respondents were white. Subjects were excluded if they had significant chronic diseases or if they had received estrogen, other steroid hormones, anticonvulsant drugs, or thiazide diuretic drugs. They were also excluded if they had taken > 500 mg Ca/d as a supplement for > 1 mo in the past year or if they had exercised for ≥ 2 h/wk in the past year. The Human Rights Committee of the University of Western Australia approved the study. Informed consent was obtained from each subject.

Weighed diet records

Subjects were given comprehensive written and verbal instructions that explained how to complete a 4-d weighed diet record. Subjects were asked to record all foods and beverages consumed for 4 consecutive days, which were randomly assigned—either Sunday through Wednesday or Tuesday through Friday. The same recording days for each subject were maintained throughout the study. Subjects were asked to record brand names when possible, methods of food preparation, and

recipes for any mixed dishes eaten during the study period. If they consumed foods and beverages away from home they were asked to use the metric cups, spoons, and grids provided or describe the foods and beverages consumed with household measures if they were unable to use the scales. At the completion of the 4-d weighed diet record, records were checked for discrepancies and omissions by a trained nutritionist or assistant. All data were analyzed by using DIET 1 nutrient calculation software (Xyris Software, Queensland, Brisbane, Australia), which uses the NUTTAB 90 database, a nutritional database of Australian foods (26). All diet records were analyzed by the same nutritionist. Values for dairy products were adjusted for calcium contents specific for Western Australia (Dairy Industry Authority, Perth, Western Australia). Values for the dietary analyses of vegetarian products were provided by the manufacturer (Sanitarium, Australia) and added to the database. Values for the dietary analyses of four Chinese meals derived from published nutrient-composition data (27) were added to the database.

The age-specific basal metabolic rate (BMR) for each subject was calculated from each subject's body weight by using the Schofield equation (28). The ratio of the average energy intake to BMR (EI:BMR) was calculated for each subject. To reduce the effect of underestimating the intake of energy and other nutrients, biased records, ie, those with EI:BMR below the limit (0.88) compatible with long-term weight maintenance defined by Goldberg et al (29) for an individual for a 4-d record, were identified and excluded from the analyses. Of the 129 subjects, 126 subjects completed a diet record at 2 y. Nine at baseline and 19 subjects at 2 y had an EI:BMR < 0.88 and these data were rejected. One subject had energy intake 3 SDs above the mean energy intake at both time points and these data were rejected. At baseline and 2 y, 119 and 106 subjects were included in the respective analyses.

Biochemical and anthropometric measurements

A blood sample was collected from each subject after they had fasted overnight. These samples were not taken during the dietary recording period. IGF-I was measured by a competitive-binding double-antibody radioimmunoassay using a kit from Nichols Corning (San Juan Capistrano, CA) after acid ethanol cryoprecipitation and extraction. Eight IGF-I runs were undertaken and eight separate assay kits were used. Paired samples from the same subject (baseline and 2 y) were run with the same kit. The intraassay CVs were 6.11%, 5.17%, 1.79%, 3.28%, 0.68%, 3.89%, 1.85%, and 4.99%. The interassay CV for the set was 5.02%. IGF-BP-3 was measured by using a two-site immunoradiometric kit (Diagnostic Systems Laboratories, Webster, TX). Three Diagnostic System Laboratories immunoradiometric kits were used for the IGF-BP-3 analyses. The intraassay CVs were 0.53%, 1.41%, and 3.61% and the interassay CV was 1.02%. IGF-BP-4 and IGF-BP-5 concentrations were measured by radioimmunoassays (23, 24). These assays showed no significant cross-reactivity with any of the other known IGF-BPs. Inter- and intraassay CVs were $< 10\%$ for both assays.

Statistical analyses

Descriptive statistics include means and SDs for the biochemical measurements and dietary intake averaged over 4 d. The percentage of subjects who achieved the recommended dietary intake (RDI) or $\geq 70\%$ of the RDI for women aged ≥ 54 y (28)

was calculated for protein and zinc. At baseline and 2 y, interrelations between dietary intakes and serum IGF-I and IGF-BPs were calculated by using Spearman's correlation coefficient. Multiple regression analysis was used to determine the significant determinants of serum IGF-I concentration at each time point. Paired sample *t* test was used to examine differences in nutrient intake and serum IGF-I and IGF-BPs between baseline and 2 y. One-way analysis of variance (ANOVA) with Duncan's new multiple-range test was used to determine the difference between treatment groups (placebo, calcium, calcium and exercise, and milk) in the change in zinc intake and change in IGF-I and IGF-BPs during the study. Duncan's test was only used if the one-way ANOVA was significant. All *P* values were two tailed at a significance level <0.05. The statistical package used was SPSSPC for Windows (SPSS, Inc, Chicago).

RESULTS

At baseline and 2 y, 119 and 106 subjects were included in respective analyses except for that of IGF-BP-3. The mean (\pm SD) age at baseline was 62.9 ± 4.4 y. The subjects were on average 15.5

± 4.8 y past menopause with an average body weight of 66 ± 9.4 kg and height of 161 ± 6.0 cm.

Nutrient intake

Baseline and 2-y mean intakes of all nutrients are listed in **Table 1**. Intakes of calcium, sodium, and phosphorus increased significantly between baseline and 2 y (Table 1). Intakes of energy, fat, cholesterol, saturated fat, iron, and fiber decreased significantly between baseline and 2 y (Table 1). At baseline and 2 y, 23% and 31% of subjects, respectively, had zinc intakes <8.4 mg/d. Most subjects (86% and 88%) had intakes below the RDI for zinc of 12 mg at baseline and 2 y, respectively. Ninety-eight percent and 100% of subjects had protein intakes greater than the RDI for protein (45 g) at baseline and 2 y, respectively.

IGF-I and nutrient intake

At baseline, positive correlations were found between IGF-I and the mean dietary intakes of several nutrients: calcium, cholesterol, energy, iron, potassium, magnesium, sodium, niacin, phosphorus, protein, riboflavin, thiamine, and zinc (**Table 2**). The significant positive correlation between dietary zinc intake and IGF-I concentration (**Figure 1**) was not influenced by the

TABLE 1

Daily intake of nutrients and the concentration of insulin-like growth factor I (IGF-I) and IGF binding proteins (BPs) in postmenopausal women at baseline and 2 y¹

	Baseline (n = 119)	2 y ² (n = 106)	RDI
Energy (kJ)	7106 \pm 1270 (4538–10674) ³	6906 \pm 1234 ⁴ (4519–9945)	7300–8400
Alcohol (g)	5.0 \pm 7.4 (0–33)	4.5 \pm 7.0 (0–35)	—
Protein (g)	78 \pm 14 (51–112)	78 \pm 17 (43–131)	45
Total carbohydrate (g)	196 \pm 44 (113–351)	194 \pm 42 (106–304)	—
Starches (g)	93 \pm 23 (45–160)	91 \pm 24 (37–171)	—
Sugars (g)	100 \pm 31 (34–217)	101 \pm 32 (24–182)	—
Fiber (g)	24 \pm 7.3 (11–45)	22 \pm 6.3 ⁴ (11–51)	—
Total fat (g)	64 \pm 18 (32–113)	60 \pm 17 ⁴ (24–118)	27–40
MUFA (g)	22 \pm 6.3 (10–40)	21 \pm 6.2 (8.0–45)	—
PUFA (g)	11 \pm 4.7 (2.3–29)	11 \pm 4.6 (2.3–29)	—
SFA (g)	26 \pm 9.0 (9.7–56)	23 \pm 8.2 ⁴ (6.4–45)	—
Cholesterol (mg)	228 \pm 94 (90–817)	207 \pm 75 ⁴ (31–427)	0–300
Calcium (mg)	857 \pm 336 (201–1984)	1492 \pm 510 ⁴ (221–2574)	1000
Phosphorus (mg)	1325 \pm 302 (761–2097)	1403 \pm 383 ⁴ (702–2357)	1000
Iron (mg)	12 \pm 3.2 (7.0–24)	11 \pm 3.0 ⁴ (6.2–23)	5–7
Potassium (mg)	3106 \pm 673 (1726–4966)	3205 \pm 801 (1447–5822)	1950–5460
Sodium (mg)	2029 \pm 565 (1028–3769)	2365 \pm 623 ⁴ (1130–4750)	920–2300
Zinc (mg)	10 \pm 2.2 (6.0–17)	9.6 \pm 2.4 (4.7–17)	12
Magnesium (mg)	306 \pm 79 (150–516)	304 \pm 80 (149–622)	270
Vitamin A (μ g RE)	1294 \pm 1688 (210–10889)	987 \pm 740 (182–6969)	750
Thiamine (mg)	1.3 \pm 0.4 (0.5–2.9)	1.3 \pm 0.4 (0.5–2.6)	0.7
Riboflavin (mg)	2.0 \pm 0.7 (0.8–4.3)	2.1 \pm 0.8 —	1.0
Niacin (mg)	18 \pm 4.6 (9.6–33.8)	17 \pm 4.8 (9.0–34)	11
Vitamin C (mg)	139 \pm 76 (35–538)	135 \pm 77 (18–419)	30
IGF-I (μ g/L)	172 \pm 57 (46–399)	142 \pm 43 ⁴ (50–297)	—
IGFBP-3 (μ g/L) ⁵	3130 \pm 777 (1383–5712)	2917 \pm 513 ⁴ (1501–3862)	—
IGFBP-4 (μ g/L)	204 \pm 102 (21–443)	313 \pm 144 ⁴ (25–700)	—
IGFBP-5 (μ g/L)	203 \pm 48 (110–336)	194 \pm 55 (27–368)	—

¹ RDI, recommended dietary intakes for selected nutrients for women ≥ 54 y (28); MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; RE, retinol equivalent.

² Intakes include the nutrient content of the intervention supplement.

³ $\bar{x} \pm$ SD; range in parentheses.

⁴ Significantly different from baseline, *P* < 0.05 (paired sample *t* test).

⁵ *n* = 43 at baseline; *n* = 39 at 2 y.

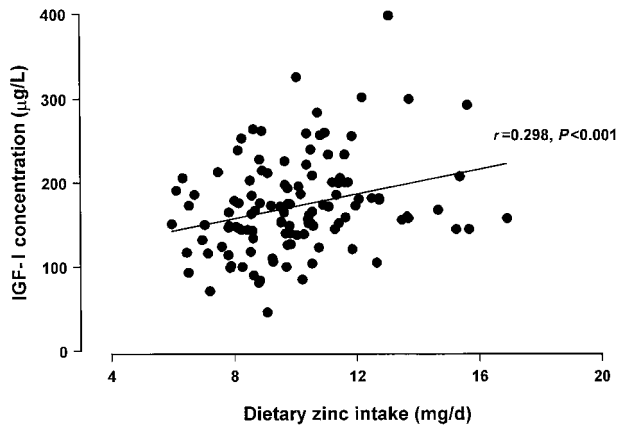


FIGURE 1. Relation between average dietary zinc intake assessed by a 4-d weighed diet record and serum insulin-like growth factor I (IGF-I) concentration in 119 postmenopausal women at baseline.

subject with an IGF-I concentration of 399 $\mu\text{g/L}$. Thus, the data point was included in the analyses. Multiple regression was performed with IGF-I concentration as the dependent variable and all nutrient intakes correlated with IGF-I in univariate analysis, age, and weight as the independent variables. The results of this analysis showed that zinc and age were the only significant determinants of IGF-I concentration (**Table 3**).

At 2 y, IGF-I was positively correlated only with dietary intakes of zinc (**Figure 2**) and protein (**Table 2**). Multiple regression was performed with IGF-I concentration measured at 2 y as the dependent variable and all mean nutrient intakes correlated with IGF-I in univariate analysis at baseline, age, weight, and treatment group as the independent variables. The results of this analysis showed that zinc was the only significant determinant of IGF-I concentration at 2 y (**Table 3**).

Paired samples of baseline and 2-y concentrations of IGF-I ($r = 0.710$, $P < 0.001$), IGFBP-3 ($r = 0.717$, $P < 0.001$), IGFBP-4 ($r = 0.235$, $P < 0.015$), and IGFBP-5 ($r = 0.430$, $P < 0.001$) were significantly positively correlated. For the whole group, IGF-I ($P < 0.001$) and IGFBP-3 ($P < 0.03$) concentrations fell over the 2 y of the study, whereas IGFBP-4 concentrations rose significantly ($P < 0.001$) (**Table 1**).

At baseline, dietary intakes of energy ($r = 0.585$, $P < 0.001$), protein ($r = 0.354$, $P < 0.001$), and zinc ($r = 0.288$, $P = 0.003$) were significantly correlated with their counterparts at 2 y. Zinc and protein intakes were highly correlated at baseline ($r = 0.793$, $P < 0.001$) and 2 y ($r = 0.885$, $P < 0.001$), more so than energy and protein intakes at baseline ($r = 0.532$, $P < 0.001$) and 2 y ($r = 0.567$, $P < 0.001$). During the 2 y, the change in zinc intake was significantly greater in the milk-supplemented group (1.27 ± 2.11 mg/d) than in the calcium and exercise (-0.63 ± 2.43 mg/d), placebo (-1.68 ± 2.87 mg/d), or calcium-supplemented groups (-0.96 ± 2.14 mg/d). However, the change in concentrations of IGF-I and the binding proteins was not significantly different between the treatment groups.

Relation between IGF-I, IGFBPs, age, and nutrient intake

The baseline and 2-y concentrations of IGF-I and the IGFBPs are reported in **Table 1**. At baseline, age was negatively

correlated with concentrations of IGF-I ($r = -0.269$, $P < 0.01$) and IGFBP-3 ($r = -0.369$, $P < 0.01$) and positively correlated with concentrations of IGFBP-4 ($r = 0.219$, $P < 0.05$). At 2 y, age was negatively correlated with only IGFBP-3 ($r = -0.432$, $P < 0.01$).

At baseline, IGF-I was significantly correlated with IGFBP-3 ($r = 0.627$, $P < 0.001$) and IGFBP-5 ($r = 0.459$, $P < 0.001$). IGFBP-3 was correlated with IGFBP-5 ($r = 0.499$, $P = 0.001$). At 2 y, IGF-I was significantly correlated with IGFBP-3 ($r = 0.424$, $P = 0.007$) and negatively correlated with IGFBP-4 ($r = 0.201$, $P = 0.039$). IGFBP-4 was correlated with IGFBP-5 ($r = 0.328$, $P = 0.001$).

At baseline, IGFBP-3 was correlated with mean riboflavin intake ($r = 0.392$, $P = 0.009$), IGFBP-4 was negatively correlated with mean phosphorus intake ($r = -0.273$, $P = 0.003$), and IGFBP-5 was positively correlated with mean sodium ($r = 0.194$, $P = 0.035$) and phosphorus ($r = 0.205$, $P = 0.026$) intakes. At 2 y, IGFBP-3 was not correlated with the mean intake of any nutrients. IGFBP-4 was correlated with mean fat intake ($r = 0.210$, $P = 0.031$) and mean saturated fat intake ($r = 0.248$, $P = 0.010$). IGFBP-5 was negatively correlated with mean vitamin C intake ($r = -0.291$, $P = 0.002$). At baseline and 2 y the IGFBPs were not consistently correlated with mean intakes of nutrients in univariate analysis and were not analyzed further by using multiple regression analyses.

DISCUSSION

These results indicate that zinc intake measured by a 4-d weighed diet record was correlated with serum IGF-I concentrations better than was protein intake or age in a group of healthy, community-dwelling postmenopausal women. Previous investigations support the association between zinc intake and IGF-I concentrations in states of malnutrition in animal models (7–9, 11, 14) and children (12, 13). Zinc deficiency reduces IGF-I concentrations and, thus, growth is compromised. With zinc supplementation, concentrations of IGF-I and growth are improved (9, 12, 13). Evidence suggests that decreased hepatic IGF-I gene expression and defects in the intracellular growth hormone–signaling pathway (8, 9, 14) occur in the zinc-deficient state, which

TABLE 2

Correlation coefficients of nutrient intake and serum insulin-like growth factor I (IGF-I) measured at baseline and 2 y

Nutrient	Baseline IGF-I		2-y IGF-I	
	<i>r</i>	<i>P</i> ¹	<i>r</i>	<i>P</i> ²
Energy (kJ)	0.192	0.036	NS	—
Protein (g)	0.313	0.001	0.256	0.008
Cholesterol (mg)	0.188	0.040	NS	—
Calcium (mg)	0.186	0.042	NS	—
Phosphorus (mg)	0.296	0.001	NS	—
Iron (mg)	0.209	0.0023	NS	—
Potassium (mg)	0.245	0.007	NS	—
Sodium (mg)	0.221	0.016	NS	—
Zinc (mg)	0.298	0.001	0.331	0.001
Magnesium (mg)	0.223	0.015	NS	—
Thiamine (mg)	0.257	0.005	NS	—
Riboflavin (mg)	0.223	0.0015	NS	—
Niacin (mg)	0.202	0.028	NS	—

¹Significance level for comparison at baseline.

²Significance level for comparison at 2 y.

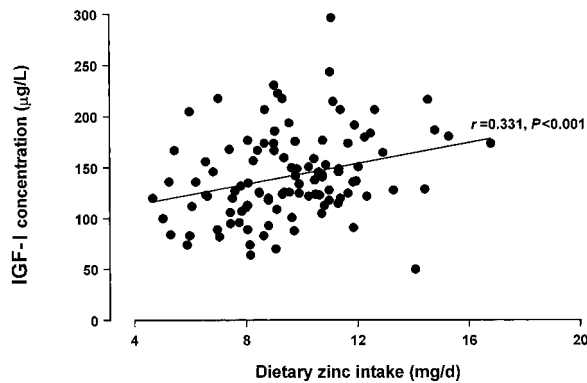


FIGURE 2. Relation between average dietary zinc intake assessed by a 4-d weighed diet record and serum insulin-like growth factor I (IGF-I) concentration in 106 postmenopausal women at 2 y.

lead to a reduction in the production of IGF-I. Even though the subjects in this study were healthy, community-dwelling individuals who ate self-selected diets, during the study one-quarter of subjects had a zinc intake <70% of the RDI (<8.4 mg) and $\geq 86\%$ of the subjects had zinc intakes below the RDI (12 mg). Mean energy intakes during the study were slightly below the recommended range for older women weighing 65 kg (7300–8400 kJ/d) (28). These intakes, however, were sufficient to be considered above the limit compatible with long-term weight maintenance defined by Goldberg et al (29). This suggests that even in women with adequate intakes of energy and protein, zinc intake influences IGF-I concentrations.

Restriction of dietary protein in animals suggests that a postreceptor defect is responsible for a reduction in IGF-I mRNA transcription leading to a reduction in IGF-I production (15). Further, the binding affinity of IGF-I to its preferential binding protein IGFBP-3 is altered in the protein-deficient state and clearance from serum is affected. In this study, protein intake was above recommendations (45 g/d; 28) made for Westernized diets (2, 18), which may explain the lack of significant relations between protein intake and IGFBP-3. These relations may have been altered if the subjects were fasting or protein deficient. Alternatively, in this study the small sample size at baseline ($n = 43$) and 2 y ($n = 39$) for IGFBP-3 may in part have accounted for the lack of significance.

The major source of zinc consumed by most individuals is animal products (51%), namely, meat and meat products (2). Cereals and milk products contribute lesser amounts, 17% and 12%, respectively (2). Previous investigation focused on the effects of macronutrients such as energy and protein on IGF-I action. After fasting, the amount of energy and quality of protein are important in the recovery of serum IGF-I concentrations (1). Moreover, protein deprivation alters the biological action and expression of IGF-I, its clearance, binding, and degradation and may increase organ-specific resistance to its growth-mediating actions. Because zinc is provided by protein foods, especially animal products, the role of zinc per se in different states of malnutrition and accompanying effects on IGF-I action has been difficult to distinguish. Zinc plays a role in the nutritional regulation of IGF-I and may have been a surrogate for the action of protein in previous investigations (1, 11). This study supports evidence that the effects of zinc intake on IGF-I concentrations may be independent of protein intake, despite the cocorrelation between zinc and protein intakes during the study.

IGF-I is a critical factor in the regulation of bone turnover (4, 30, 31). Changes in serum concentrations of IGF-I may occur because of inadequate dietary sources of nutrients such as zinc, which are common (2, 16, 18). Moreover, skeletal IGF-I concentrations are positively correlated with serum IGF-I and negatively correlated with age (3, 5), as supported by this study. These factors suggest that age-related bone loss may be associated with reductions in local and systemic concentrations of IGF-I associated with reduced nutrient intake. Evidence of hyperzincuria in osteoporotic patients was reported (20). Taken together with inadequate zinc intake and increased bone resorption, postmenopausal women are at increased risk of reducing their zinc status. Paradoxically, the zinc released by bone resorption may actually tend to protect elderly women from a reduced zinc intake. These findings warrant further investigation into the relation of zinc intake, IGF-I, and bone health.

The nutritional regulation of IGF-BPs in fasting and chronic dietary restriction has been reviewed extensively (15, 32). Differences in abundance of the binding proteins occur in dietary restriction. Organ specificity is also important in their regulation. Reductions in IGFBP-3 have been noted in dietary restriction and plasma IGF-I clearance is increased in conditions in which IGFBP-3 is reduced. During the study, those subjects consuming a daily milk supplement had a significant rise in zinc intake that was not paralleled by an increase in IGF-I or IGFBP-3. Correlations with IGFBP-4 and IGFBP-5 were not

TABLE 3

Multiple regression analysis of serum insulin-like growth factor I (IGF-I) with weight, age, and mean intake of selected nutrients¹

	Regression coefficient	SE of the regression coefficient	Standardized regression coefficient	Significance of <i>F</i> value
Baseline IGF-I ²				
+ Zinc intake	6.90	2.27	0.265	0.0029
- Age	2.71	1.12	-0.21	0.0172
+ Constant	273.18	76.01	—	—
2-y IGF-I ³				
+ Zinc intake	5.15	1.71	0.28	0.0033
- Constant	92.40	16.87	—	—

¹ Nutrients correlated with IGF-I in univariate analysis at baseline included as independent variables at baseline and 2 y.


² $R = 0.35$.

³ Treatment group included as an independent variable in the 2-y analysis. $R = 0.28$.

consistent with nutrient intake. Research suggests that the exact action of the binding proteins is not known, but in protein restriction, differential regulation of IGFBP mRNAs and peptides exists (15). Further investigation into IGFBP concentrations and nutrient interactions in healthy postmenopausal women is required.

A shortcoming of this study was the lack of measurement of IGFBP-1, which is regulated by protein and calcium intake, and which may regulate IGF-I bioactivity. Serum zinc concentrations were not measured either and would have provided more presumptive evidence that zinc and IGF-I are linked. The effect of IGF-I and zinc intake may be underestimated in this population because of the healthy nature of the subjects. If the population were extended to include frail elderly, in whom nutrient intake may be even lower, a wider range of serum IGF-I values would be expected and a more positive effect (*r* value) would be seen across a range of nutrient intakes and expressions of serum IGF-I.

The effect of calcium supplementation from a food source or tablet was studied in this population and described in detail elsewhere (33). Significant changes in nutrient intake were reflected in dietary intake data and were related to the type of intervention. Significant correlations between baseline and 2-y intakes of energy, protein, and zinc suggest that individuals consume similar diets over time even when taking part in a calcium intervention trial. Recently, Wood and Zheng (34) reported a detrimental effect of concurrent calcium supplementation on zinc absorption that may be offset by zinc being included in the calcium supplement. If high-calcium diets reduce zinc absorption and balance, it may therefore be necessary to further increase the requirements for zinc in elderly postmenopausal women. However, in this study the calcium supplement was not administered with food.

In conclusion, this study extends the associations between zinc intake and serum IGF-I concentration seen in the nutrient-restricted animal models and children to healthy postmenopausal women. Furthermore, intakes of certain nutrients, primarily zinc and protein, assessed by a weighed diet record correlated with IGF-I concentrations at two different time points. After age, weight, and other nutrient intakes were adjusted for, zinc intake remained the major determinant of IGF-I concentration. This study provides additional evidence from 4-d weighed diet record data of the association between zinc intake and IGF-I concentrations. Even though dietary records are associated with user and interpreter errors (35), they have proved to be a tool able to elicit a relation previously seen in studies of malnourished animals and children. These findings warrant further investigation into the relation of zinc intake with IGF-I and health in an aging population. 

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REFERENCES

- Ketelslegers JM, Maiter D, Maes M, Underwood LE, Thissen JP. Nutritional regulation of insulin-like growth factor-I. *Metabolism* 1995;44(suppl):50-7.
- Department of Community Services and Health. National dietary survey of adults: 1983, no. 2. Nutrient intakes. 1st ed. Canberra, Australia: Australian Government Publishing Service, 1987.
- Rudman D. Growth hormone, body composition, and aging. *J Am Geriatr Soc* 1985;33:800-7.
- Blumsohn A, Eastell R. Age related factors. In: Riggs BL, Melton LJ, eds. *Osteoporosis: etiology, diagnosis and management*. 2nd ed. Philadelphia: Lippincott-Raven Publishers, 1995:173-4.
- Nicolas V, Prewett A, Bettica P, et al. Age-related decreases in insulin-like growth factor-I and transforming growth factor- β in femoral cortical bone from both men and women: implications for bone loss with aging. *J Clin Endocrinol Metab* 1994;78:1011-6.
- Bennett AE, Wahner HW, Riggs BL, Hintz RL. Insulin-like growth factors I and II: aging and bone density in women. *J Clin Endocrinol Metab* 1984;59:701-4.
- Droke EA, Spears JW, Armstrong JD, Kegley EB, Simpson RB. Dietary zinc affects serum concentrations of insulin and insulin-like growth factor I in growing lambs. *J Nutr* 1993;123:13-9.
- McNall AD, Etherton TD, Fosmire GJ. The impaired growth induced by zinc deficiency in rats is associated with decreased expression of the hepatic insulin-like growth factor I and growth hormone receptor genes. *J Nutr* 1995;125:874-9.
- Dorup I, Flyvbjerg A, Everts ME, Clausen T. Role of insulin-like growth factor-I and growth hormone in growth inhibition induced by magnesium and zinc deficiencies. *Br J Nutr* 1991;66:505-21.
- Roth HP, Kirchgessner M. Influence of alimentary zinc deficiency on the concentration of growth hormone (GH), insulin-like growth factor I (IGF-I) and insulin in the serum of force-fed rats. *Horm Metab Res* 1994;26:404-8.
- Clegg MS, Keen CL, Donovan SM. Zinc deficiency-induced anorexia influences the distribution of serum insulin-like growth factor-binding proteins in the rat. *Metabolism* 1995;44:1495-501.
- Nakamura T, Nishiyama S, Futagoishi-Suginohara Y, Matsuda I, Higashi A. Mild to moderate zinc deficiency in short children: effect of zinc supplementation on linear growth velocity. *J Pediatr* 1993;123:65-9.
- Ninh NX, Thissen JP, Collette L, Gerard G, Khoi HH, Ketelslegers JM. Zinc supplementation increases growth and circulating insulin-like growth factor I (IGF-I) in growth-retarded Vietnamese children. *Am J Clin Nutr* 1996;63:514-9.
- Ninh NX, Thissen JP, Maiter D, Adam E, Mulumba N, Ketelslegers JM. Reduced liver insulin-like growth factor-I gene expression in young zinc-depleted rats is associated with a decrease in liver growth hormone (GH) receptors and serum GH-binding protein. *J Endocrinol* 1995;144:449-56.
- Underwood LE, Thissen JP, Lemozy S, Ketelslegers JM, Clemmons DR. Hormonal and nutritional regulation of IGF-I and its binding proteins. *Horm Res* 1994;42:145-51.
- Devine A, Prince RL, Bell RR. Nutrient intake of postmenopausal women in relation to skeletal and cardiovascular disease. *Aust J Nutr Diet* 1996;53:144-50.
- Baghurst KI, Hope AK, Down EC. Dietary intake in a group of institutionalised elderly and the effect of a fibre supplementation programme on nutrient intake and weight gain. *Community Health Studies* 1985;9:99-108.
- Payette H, Gray-Donald K. Dietary intake and biochemical indices of nutritional status in an elderly population, with estimates of the precision of the 7-d food record. *Am J Clin Nutr* 1991;54:478-88.
- Sandstead HH, Henriksen LK, Greger JL, Prasad AS, Good RA. Zinc nutrition in the elderly in relation to taste acuity, immune response, and wound healing. *Am J Clin Nutr* 1982;36:1046-59.
- Herzberg M, Foldes J, Steinberg R, Menczel J. Zinc excretion in osteoporotic women. *J Bone Miner Res* 1990;3:251-7.
- Simmons DJ. *Nutrition and bone development*. New York: Oxford University Press, 1990.
- Mohan S, Nakao Y, Honda Y, et al. Studies on the mechanisms by which insulin-like growth factor (IGF) binding protein-4 (IGFBP-4) and IGFBP-5 modulate IGF actions in bone cells. *J Biol Chem* 1995;270:20424-31.
- Honda Y, Landale EC, Strong DD, Baylink DJ, Mohan S. Recombinant synthesis of insulin-like growth factor-binding protein-4 (IGFBP-4): development, validation, and application of a radioimmunoassay for IGFBP-4 in human serum and other biological fluids. *J Clin Endocrinol Metab* 1996;81:1389-96.

24. Mohan S, Libanati C, Dony C, Lang K, Srinivasan N, Baylink DJ. Development, validation, and application of a radioimmunoassay for insulin-like growth factor binding protein-5 in human serum and other biological fluids. *J Clin Endocrinol Metab* 1995;80:2638–45.
25. Prince R, Devine A, Dick I, et al. The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. *J Bone Miner Res* 1995;10:1068–75.
26. Department of Community Services and Health. Nuttab 90. Canberra, Australia: Australian Government Publishing Service, 1990.
27. Greenfield H, Wimalasiri P, Han LTN, Balmer N, Wills RBH. Composition of Australian foods 6. Chinese foods. *Food Technol Aust* 1981;33:176–81.
28. National Health and Medical Research Council. Recommended dietary intakes for use in Australia. Canberra, Australia: Australian Government Publishing Service, 1991.
29. Goldberg GR, Black AE, Jebb SA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. *Eur J Clin Nutr* 1991;45:569–81.
30. Ebeling PR, Jones JD, O'Fallon WM, Janes CH, Riggs BL. Short-term effects of recombinant human insulin-like growth factor I on bone turnover in normal women. *J Clin Endocrinol Metab* 1993;77:1384–7.
31. Grinspoon SK, Baum HB, Peterson S, Klibanski A. Effects of rhIGF-I administration on bone turnover during short-term fasting. *J Clin Invest* 1995;96:900–6.
32. Thissen J, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. *Endocr Rev* 1994;15:80–101.
33. Devine A, Prince RL, Bell R. Nutritional effect of calcium supplementation by skim milk powder or calcium tablets on total nutrient intake in post menopausal women. *Am J Clin Nutr* 1996;64:731–7.
34. Wood RJ, Zheng JJ. High dietary calcium intakes reduce zinc absorption and balance in humans. *Am J Clin Nutr* 1997;65:1803–9.
35. Willett W. *Nutritional epidemiology*. New York: Oxford University Press, Inc, 1990.