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Short-Term Low-Protein Intake Does Not Increase Serum Parathyroid Hormone Concentration in Humans[1,2]

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Abstract

We investigated whether inadequate dietary protein would result in increased serum parathyroid hormone (PTH) concentration, consistent with secondary hyperparathyroidism. Data from 2 controlled feeding studies were utilized. In study 1, 26 healthy women (15 young, 21–46 y, and 11 elderly, 70–81 y) consumed for 12 d each in separate trials 3 levels of protein, 1.00, 0.75, and 0.50 g protein/(kg · d). Blood was drawn from fasting subjects on d 12 of each trial. In study 2, 24 persons (54–80 y) were fed diets with either 1.20 g protein/(kg · d) for 2 wk (HPro, *n* = 11, 6 men, 5 women) or 1.2 g protein/(kg · d) for 1 wk and then 0.50 g protein/(kg · d) for a 2nd week (IPro, *n* = 13, 6 men, 7 women). Blood was obtained from fasting subjects after wk 1 and 2. Consistent with altered protein metabolism, urinary total nitrogen excretion and blood urea nitrogen fell progressively with decreasing protein intake in study 1; in study 2, the values decreased from wk 1 to 2 in the IPro group only. Serum intact PTH concentrations did not differ among the 3 protein intakes in study 1, or between the HPro and IPro groups in study 2. These findings do not support the hypothesis that the short-term ingestion of inadequate dietary protein increases serum PTH concentration.

Keywords

calcium; elderly; protein adequacy; hyperparathyroidism

Dietary protein affects calcium metabolism and may affect longer-term bone homeostasis (1, 2). One line of thinking is that high dietary protein intake promotes urinary calcium loss and contributes to negative calcium balance and osteoporosis (3). In contrast, Hannan et al. (4) found that elderly men and women with relatively lower protein intake had increased bone loss at the femoral neck and spine over a 4-y period. Although this suggests that maintaining higher protein intake was important for maintaining bone and minimizing bone loss in elderly persons, a mechanism for this effect has not been demonstrated. A few provocative studies recently

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reported that protein intakes at or somewhat below the Recommended Dietary Allowance (RDA)[4] of 0.8 g protein/(kg · d) for as short a period as 4 d resulted in decreased calcium absorption, increased serum parathyroid hormone (PTH) concentrations (in some cases exceeding clinical normalcy consistent with secondary hyperparathyroidism), and increased serum calcitriol concentrations (5–8). The strikingly quick onset and apparent consistency of these indices of secondary hyperparathyroidism in response to protein intakes less than or equal to the RDA (5–7) suggest that the RDA for protein negatively affects short-term calcium homeostasis (2). This condition could be reversed by increasing dietary protein intake. Further investigation of the potentially detrimental effect of inadequate protein intake on calcium metabolism and bone health is warranted (9,10), including more evaluations of a possible relation between protein intake and parathyroid hormone. Our objective was to determine whether broad changes in dietary protein intake that span the range of adequacy would alter serum PTH concentration. The results from 2 controlled feeding studies are reported.

Subjects and Methods

Study 1: subjects

Fifteen premenopausal women, age 32 ± 8 y (mean ± SD; range 21–46 y), and 11 postmenopausal women, age 74 ± 4 y (range 70–81 y) participated in this study. Each woman completed a prestudy medical evaluation that included a written medical history, a resting-state electrocardiogram, and routine blood and urine chemistries, and signed a written informed consent agreement. The study protocol and consent form were reviewed and approved by the Human Research Advisory Committee, University of Arkansas for Medical Sciences and by the Committee on the Use of Human Research Subjects, Purdue University.

Study 1: experimental design

A 3-trial randomized crossover study was completed, with all measurements made from d 7–12 of each trial, as described below. The experimental conditions were the same during each trial, except that each woman consumed a different amount of dietary protein. A minimum 1-wk washout period occurred between the trials during which each woman consumed her habitual diet. Blood samples from fasting subjects were obtained from an anticubital vein on d 12 of each trial. Four 24-h urine collections were made on d 7–10 of each trial.

Study 1: diet

Throughout each trial the women were provided foods and beverages, using a rotating schedule of 3 menus that contained a total energy content equal to 1.75 times the resting energy expenditure, predicted from the Harris-Benedict equation for women (11). The protein intake during each trial was set at 1.00 g protein/(kg · d) (adequate protein intake, APro, 125% of RDA), 0.75 g protein/(kg · d) (marginal protein intake, MPro, 94% of RDA), or 0.50 g protein/(kg · d) (inadequate protein intake, IPro, 63% of RDA). Animal muscle tissues were not provided in the menus due to their higher protein contents, although animal-based proteins were provided in the forms of dairy and egg-based proteins. The nonprotein energy content of each of the 3 diets was kept constant at 65% carbohydrate and 35% fat. To enhance adaptation to the subsequent protein intake (12), each subject consumed for 1 d at the start of each trial a diet that contained 0.2 g protein/(kg · d). Each subject was required to abstain from consuming alcohol and using salt-containing seasonings throughout the 3 trials. The energy, protein, carbohydrate, fat, fiber, calcium, phosphorus, vitamin D, and sodium contents of the menus were calculated using Nutritionist Pro computer software (First Databank) (Table 1). Each

[4]Abbreviations used: APro, adequate protein intake; HPro, higher protein intake; IPro, inadequate protein intake; MPro, marginal protein intake; NcAMP, nephrogenous cyclic adenosine monophosphate; PTH, parathyroid hormone; RDA, Recommended Dietary Allowance.

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woman consumed weekday morning meals under supervision at our dining facility and all remaining meals were packaged to take home. All dishes, glassware, and utensils were scraped and rinsed with water and the rinsings consumed. Each woman consumed daily 1 multivitamin-multimineral supplement tablet (Advanced Formula Centrum, Lederle Laboratories).

Study 2: subjects

Twelve postmenopausal women, age 65 ± 6 y (range 55–76 y) and 12 men, age 67 ± 9 y (range 54–80 y) participated in this study. Preceding the study, each participant completed an evaluation that included a written medical history, a resting-state electrocardiogram, and routine blood and urine chemistries, and signed a written informed consent agreement. The study protocol and consent form were reviewed and approved by the Committee on the Use of Human Research Subjects, Purdue University.

Study 2: experimental design

Each participant completed a continuous 2-wk controlled diet period, with measurements made at the end of wk 1 and 2. The participants were randomly assigned to 1 of 2 dietary treatments, as described below. Blood samples were obtained from fasting subjects from an anticubital vein on d 7 and 14; 24-h urine collections were made on d 5, 6, 12, and 13.

Study 2: diet

During wk 1, all of the participants consumed a diet that provided 1.2 g protein/(kg · d). During wk 2, 6 men and 5 women continued to consume the diet that contained 1.2 g protein/(kg · d) (higher protein intake, HPro, 150% of RDA), and 6 men and 7 women consumed a diet that contained 0.2 g protein/(kg · d) for 1 d, followed by a diet that contained 0.5 g protein/(kg · d) for the remainder of the study (inadequate protein intake, IPro, 63% of RDA). The 1-d very low protein menu was used to enhance adaptation to the subsequent protein intake (12). Each participant's menus were individualized to contain sufficient energy for body weight maintenance and a nonprotein energy content of 65% carbohydrate and 35% fat, were muscle-tissue-free, and contained animal-based proteins from dairy and egg sources. The subjects were not allowed to use salt-containing seasonings or consume alcohol during the study. The energy, protein, carbohydrate, fat, fiber, calcium, phosphorus, vitamin D, and sodium contents of the menus were calculated using Nutritionist Pro computer software (First Databank) (Table 2). The setting (i.e., at or away from the laboratory dining facility), the procedures for consuming the meals (i.e., scraping and rinsing), and the daily ingestion of 1 multivitamin-multimineral supplement tablet were the same as those described for study 1.

Laboratory methods

For both studies, serum intact PTH concentrations were measured using an immunochemiluminometric assay at Laboratory Corporation of America (LabCorp). Serum blood urea nitrogen concentrations were measured using the urease/glutamate dehydrogenase coupled enzymatic technique at the Pathology and Laboratory Medicine Service, Central Arkansas Veterans Healthcare System, Little Rock, AR or at Labcorp. Urinary total nitrogen concentrations were measured using a nitrogen analyzer (model FP-528, Leco).

Statistical methods

Values are reported as means ± SD. Data were analyzed using the JMP Statistical Discovery Software (SAS Institute). Differences between groups and at different time points were assessed using repeated-measures ANOVA. Differences were considered significant at $P < 0.05$. Data from 1 man assigned to the high protein group in study 2 were excluded from the analyses because his serum PTH concentration at wk 1 was above clinical normalcy.

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Results

Study 1

The group of younger women consumed greater absolute amounts of energy ($P < 0.001$), carbohydrate ($P < 0.001$), and fat ($P < 0.001$) than the group of elderly women, consistent with greater energy needs (Table 1). The absolute and relative amounts of protein intake did not differ between the young and elderly women. Fiber intake was higher, calcium intake was lower, and phosphorus, vitamin D, and sodium intakes did not differ in the younger vs. elderly women. For the younger and elderly women together, dietary protein intake was decreased in those consuming the APro to MPro to IPro diets ($P < 0.001$). The intakes of calcium ($P < 0.001$), phosphorus ($P < 0.001$), and sodium ($P < 0.001$) also decreased in those consuming the APro to MPro to IPro diets.

For all 3 trials together, urinary total nitrogen excretion ($P < 0.05$) and blood urea nitrogen ($P < 0.001$) were lower in the younger women than in the elderly women (Table 3). For all women together, urinary total nitrogen excretion and blood urea nitrogen decreased in those consuming the APro to MPro to IPro diets ($P < 0.001$). Intact PTH did not differ between the younger and elderly women, and was not different among the 3 protein intakes.

Study 2

The dietary intakes of energy, protein, carbohydrate, fat, fiber, calcium, phosphorus, vitamin D, and sodium did not differ between the HPro and IPro groups at wk 1, and did not change for the HPro group at wk 2 (Table 2). For the IPro group, the intakes of protein, fiber, calcium, phosphorus, and sodium decreased and the intakes of carbohydrate and fat increased at wk 2.

Urinary total nitrogen excretion and blood urea nitrogen did not differ between the HPro and IPro groups at wk 1. From wk 1 to 2, they were unchanged in the HPro group and decreased in the IPro group, consistent with dietary compliance and altered protein metabolism (Table 4). Intact PTH did not differ between the HPro and IPro groups at wk 1, and was not changed in either group at wk 2.

Discussion

The primary finding of these studies is that short-term, inadequate protein intake did not increase serum intact PTH concentrations. Our data conflict with previous research (5–7). Kerstetter et al. (5) reported that serum intact and mid-molecule PTH concentrations were significantly increased in young women at 4 and 14 d after switching from a 1.0 g protein/(kg · d) to a 0.7 g protein/(kg · d) diet. These responses were not observed in the same women when they continued to consume a 1.0 g protein/(kg · d) diet or when they were switched to a 2.1 g protein/(kg · d) diet (263% of the RDA) during 14-d testing periods. Other acute responses to the 0.7 g protein/(kg · d) diet included increased serum nephrogenous cyclic adenosine monophosphate (NcAMP) concentration (a marker of PTH bioactivity), increased serum calcitriol concentration, no change in fractional calcium absorption, but a modest decrease in urinary calcium excretion (despite constant dietary intake). The midmolecule PTH, NcAMP, and calcitriol concentrations approached or exceeded the respective upper limits of clinical normalcy in response to the low-protein diet. These findings are consistent with secondary hyperparathyroidism except that no adaptation was observed in fractional calcium absorption (i.e., increased absorption normally occurs in response to elevated calcitriol concentration). Later, this same research group identified the apparent hyperparathyroid response at a threshold between 0.8 and 0.9 g protein/(kg · d) (7). Consistent with the findings of Kerstetter's group, Giannini et al. (8) reported that in 18 patients with idiopathic hypercalciuria and renal calculi

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who decreased their protein intake to the RDA [0.8 g protein/(kg · d)] for 15 d, intact PTH concentration increased 22%.

On the basis of their data, Kerstetter et al. (6) hypothesized that reduced calcium absorption is the primary consequence of low protein intake. This, in turn, would lead to a decline in serum calcium and cause a compensatory increase in PTH secretion and increased renal calcitriol production. However, although this model fits their data, the decline in intestinal calcium absorption concurrent with increased serum calcitriol levels is inconsistent with the well-characterized ability of calcitriol to stimulate intestinal calcium absorption (13,14). Kerstetter et al. (5) also noted that their data on the effect of dietary protein on serum PTH contrasts with data in men and postmenopausal women. Finally, the Kerstetter model (5) is not supported by previous data by Hannan et al. (4) or Dawson-Hughes and Harris (15) in elderly men and women. Although both of these experiments showed that lower dietary protein intakes are associated with increased bone loss, this effect did not differ significantly between the lowest tertile [0.89 ± 0.28 g protein/(kg · d); Dawson-Hughes and Harris (15)] or quartile [0.24–0.71 g protein/(kg · d); Hannon et al. (4)], which were at or lower than the RDA, and the next highest tertile/quartile, [i.e., a range similar to that studied by Kerstetter et al.; 0.72–0.96 g protein/(kg · d) in Hannon et al. (4); 1.08 ± 0.37 g protein/(kg · d) in Dawson-Hughes and Harris (15)]. In addition, the study of Dawson-Hughes and Harris (15) showed higher intestinal calcium absorption ($P < 0.05$) and lower serum PTH (nonsignificant) in subjects within the lowest tertile of dietary protein intake. The lack of agreement between the Kerstetter data (5–7) and these trials may reflect differences in the physiologic response to acute changes in dietary protein intake (i.e., Kerstetter's group) vs. chronic consumption of diets of different protein content [Hannon et al. (4) or Dawson-Hughes and Harris (15)] or the age of the study groups. Although this suggests that the phenomenon might be specific to young women or acute interventions, the results from our study 1, in which the effect of acute changes in protein intake was not noted in either young or elderly women, do not support this contention.

A weakness in our study design was that dietary calcium, phosphorus, and sodium intakes were not well controlled. The diets used in our studies were specifically formulated to control protein intake, the nonprotein macronutrient distribution, and energy, but not other nutrients. As a result, diets with lower dietary protein were also lower in calcium, phosphorus, and sodium. This is similar to a study previously reported by Shapses et al. (16) who showed that urinary markers of bone resorption did not change when dietary protein was increased from 0.44 to 2.71 g protein/(kg · d) for 5 d. This dietary change was also associated with an increase in dietary calcium from 423 to 1589 mg/d, which prompted Kerstetter et al. (17) to caution that the variability in calcium intake might obscure an effect of dietary protein on bone resorption. Although controlling the intake of these nutrients at constant levels would have improved dietary control in both our study and the earlier study by Shapses et al. (16), the direction of the error would not compensate for the proposed effect of low dietary protein intake on PTH; instead, it would have increased the likelihood of an abnormal PTH response [i.e., low dietary calcium intake promotes secondary hyperparathyroidism in humans (14)]. The fact that PTH was not elevated when low-protein diets were consumed even in the face of low dietary calcium intake suggests that the low dietary protein phenomenon is not real.

In conclusion, the results from these 2 studies indicate that the consumption of inadequate dietary protein for 1 to 2 wk does not adversely affect intact PTH or result in clinical hyperparathyroidism in younger and older humans.

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Table 1

Dietary intakes of younger and elderly women during adequate, marginal, and inadequate protein intake trials in study 1[1]

Variable	Age	APro[2]	Mpro	IPro
Energy,[3] *MJ/d*	Young	10.35 ± 0.71	10.37 ± 0.75	10.24 ± 0.63
	Elderly	9.09 ± 0.88	9.08 ± 0.88	9.06 ± 0.87
Protein,[4] *g/d*	Young	64 ± 9[a]	48 ± 6[b]	32 ± 4[c]
	Elderly	72 ± 12[a]	54 ± 9[b]	35 ± 6[c]
Carbohydrate,[3,4] *g/d*	Young	361 ± 26[b]	373 ± 29[a]	377 ± 23[a]
	Elderly	293 ± 27[c]	304 ± 27[b]	321 ± 29[a]
Fat,[3,4] *g/d*	Young	86 ± 5c	88 ± 6[b]	90 ± 6[a]
	Elderly	73 ± 7[b]	77 ± 7[a]	76 ± 7[a]
Fiber,[3] *g/d*	Young	24 ± 2	22 ± 1	20 ± 2
	Elderly	18 ± 2	18 ± 2	19 ± 2
Calcium,[3–5] *mg/d*	Young	786 ± 171[a]	650 ± 147[b]	554 ± 115[c]
	Elderly	951 ± 113[a]	761 ± 103[b]	617 ± 68[c]
Phosphorus,[4,5] *mg/d*	Young	951 ± 80[a]	823 ± 72[b]	673 ± 66[c]
	Elderly	903 ± 115[a]	767 ± 91[b]	625 ± 94[c]
Vitamin D,[5] *IU*	Young	413 ± 4	413 ± 4	413 ± 3
	Elderly	415 ± 3	418 ± 3	417 ± 3
Sodium,[4] *mg/d*	Young	4835 ± 324[a]	4375 ± 438[b]	3742 ± 523[c]
	Elderly	4513 ± 460[a]	4447 ± 405[a]	4157 ± 471[b]

[1] Values are means ± SD, $n = 15$ (young) and $n = 11$ (elderly) women. Means in a row with superscripts without a common letter differ, $P < 0.05$.

[2] APro is adequate protein intake, 1.00 g protein/(kg · d); MPro is marginal protein intake, 0.75 g protein/(kg · d); and IPro is inadequate protein intake, 0.50 g protein/(kg · d).

[3] Statistical age effect, i.e., young and elderly subjects differed when data from all 3 trials were considered together, $P < 0.05$.

[4] Statistical trial effect, i.e., the APro, MPro, and IPro trials differed when data from the young and elderly women were considered together, $P < 0.05$.

[5] Total amounts provided from diet and multivitamin-multimineral supplement.

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Table 2

Dietary intakes of older humans with higher and inadequate protein intakes in study 2[1]

Variable	Group[2]	Week 1	Week 2
Energy, *MJ/d*	HPro	9.47 ± 1.37	9.47 ± 1.37
	IPro	9.59 ± 1.49	9.49 ± 1.49
Protein,[3] *g/d*	HPro	87 ± 17	87 ± 17
	IPro	94 ± 18[a]	39 ± 7[b]
Carbohydrate,[3] *g/d*	HPro	315 ± 46	315 ± 46
	IPro	314 ± 48[b]	345 ± 55[a]
Fat,[3] *g/d*	HPro	73 ± 10	73 ± 10
	IPro	73 ± 11[b]	81 ± 12[a]
Fiber,[3] *g/d*	HPro	22 ± 3	22 ± 3
	IPro	24 ± 4[a]	19 ± 3[b]
Calcium,[3,4] *mg/d*	HPro	955 ± 143	955 ± 143
	IPro	1005 ± 155[a]	560 ± 63[b]
Phosphorus,[3,4] *mg/d*	HPro	1088 ± 174	1088 ± 174
	IPro	1159 ± 159[a]	588 ± 107[b]
Vitamin D,[4] *IU*	HPro	411 ± 4	411 ± 4
	IPro	412 ± 3	413 ± 3
Sodium,[3] *mg/d*	HPro	3970 ± 349	3970 ± 349
	IPro	4177 ± 341[a]	2695 ± 296[b]

[1] Values are means ± SD, $n = 10$ (HPro group); $n = 13$ (IPro group). Means in a row with superscripts without a common letter differ, $P < 0.05$.

[2] HPro is higher protein intake, 1.2 g protein/(kg · d) during wk 1 and 2; IPro is inadequate protein intake, 1.2 g protein/(kg · d) during wk 1 and 0.5 g protein/(kg · d) during wk 2.

[3] Group-by-time interaction, $P < 0.0001$.

[4] Total amounts provided from diet and multivitamin-multimineral supplement.

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Table 3

Urinary nitrogen excretion, blood urea nitrogen, and serum parathyroid hormone of younger and elderly women during adequate, marginal, and inadequate protein intakes in study 1[1]

Variable	Age	APro[2]	Mpro	IPro
Urinary nitrogen,[3,4] *g/d*	Young	7.3 ± 1.6[a]	5.3 ± 1.3[b]	4.8 ± 1.4[c]
	Elderly	8.6 ± 1.6[a]	6.6 ± 1.5[b]	5.1 ± 0.9[c]
Blood urea nitrogen,[3,4] *mg/dL*	Young	9 ± 2[a]	7 ± 2[b]	6 ± 1[c]
	Elderly	14 ± 4[a]	11 ± 2[b]	8 ± 3[c]
Intact PTH, *pg/mL*	Young	32 ± 12	34 ± 11	34 ± 10
	Elderly	38 ± 17	39 ± 16	35 ± 13

[1] Values are means ± SD, n = 15 (young) and 11 (elderly) women. Means in a row with superscripts without a common letter differ, $P < 0.05$. Conversion factors: urinary nitrogen, g/d × 71.38 = mmol/d; blood urea nitrogen, mg/dL × 0.357 = mmol/L; intact PTH, pg/mL × 0.106 = pmol/L.

[2] APro is adequate protein intake, 1.00 g protein/(kg · d); MPro is marginal protein intake, 0.75 g protein/(kg · d) and IPro is inadequate protein intake, 0.50 g protein/(kg · d).

[3] Statistical age effect, i.e., young and elderly subjects differed when data from all 3 trials were considered together, $P < 0.05$.

[4] Statistical trial effect, i.e., the APro, MPro, and IPro trials differed when data from the young and elderly women were considered together, $P < 0.05$.

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Table 4

Urinary nitrogen excretion, blood urea nitrogen and serum parathyroid hormone of older humans with higher or inadequate protein intakes in study 2[1]

Variable	Group[2]	Week 1	Week 2
Urinary nitrogen,[3] *g/d*	HPro	11.5 ± 2.3	11.2 ± 2.3
	IPro	11.9 ± 2.7[a]	6.1 ± 2.4[b]
Blood urea nitrogen,[3,] *mg/dL*	HPro	17 ± 3	17 ± 3
	IPro	18 ± 5[a]	11 ± 3[b]
Intact PTH, *pg/mL*	HPro	56 ± 17	55 ± 22
	IPro	51 ± 19	50 ± 16

[1] Values are means ± SD, n = 10 (HPro) and 13 (IPro) group. Means in a row with superscripts without a common letter differ, $P < 0.05$. Conversion factors: urinary nitrogen, g/d × 71.38 = mmol/d; blood urea nitrogen, mg/dL × 0.357 = mmol/L; intact PTH, pg/mL × 0.106 = pmol/L.

[2] HPro is higher protein intake, 1.2 g protein/(kg · d) during weeks 1 and 2; IPro is inadequate protein intake, 1.2 g protein/(kg · d) during wk 1 and 0.5 g protein/(kg · d) during wk 2.

[3] Group-by-Time interaction, $P < 0.0001$.