Relationship Between Serum Parathyroid Hormone Levels, Vitamin D Sufficiency, and Calcium Intake

Laufey Steingrimsdottir, PhD
Orvar Gunnarsson, MD
Olafur S. Indridason, MD, MHS
Leifur Franzson, MSc, Pharm
Gunnar Sigurdsson, MD, PhD

THE IMPORTANCE OF ADEQUATE vitamin D status for optimum bone health has received increased recognition in recent years, with higher recommended intake levels being proposed by some investigators.[1-3] The ideal intake is not known, and different criteria have been proposed for estimating population requirements. Serum 25-hydroxyvitamin D has been the generally accepted indicator of vitamin D status, but no universal consensus has been reached regarding which serum values constitute sufficiency.[4,5] A further difficulty in assigning a universal reference value may lie in the interrelationship between several factors influencing calcium homeostasis, not the least being the 2 nutrients vitamin D and calcium.

An inverse relationship between serum 25-hydroxyvitamin D and serum parathyroid hormone (PTH) is well established, up to a certain level of 25-hydroxyvitamin D, in which little further decrease in serum PTH is observed. The serum level for 25-hydroxyvitamin D corresponding with the PTH inflection point has been interpreted as

Context Adequate vitamin D status for optimum bone health has received increased recognition in recent years; however, the ideal intake is not known. Serum 25-hydroxyvitamin D is the generally accepted indicator of vitamin D status, but no universal reference level has been reached.

Objective To investigate the relative importance of high calcium intake and serum 25-hydroxyvitamin D for calcium homeostasis, as determined by serum intact parathyroid hormone (PTH).

Design, Setting, and Participants Cross-sectional study of 2310 healthy Icelandic adults who were divided equally into 3 age groups (30-45 years, 50-65 years, or 70-85 years) and recruited from February 2001 to January 2003. They were administered a semi-quantitative food frequency questionnaire, which assessed vitamin D and calcium intake. Participants were further divided into groups according to calcium intake (<800 mg/d, 800-1200 mg/d, and >1200 mg/d) and serum 25-hydroxyvitamin D level (<10 ng/mL, 10-18 ng/mL, and >18 ng/mL).

Main Outcome Measure Serum intact PTH as determined by calcium intake and vitamin D.

Results A total of 944 healthy participants completed all parts of the study. After adjusting for relevant factors, serum PTH was lowest in the group with a serum 25-hydroxyvitamin D level of more than 18 ng/mL but highest in the group with a serum 25-hydroxyvitamin D level of less than 10 ng/mL. At the low serum 25-hydroxyvitamin D level (<10 ng/mL), calcium intake of less than 800 mg/d vs more than 1200 mg/d was significantly associated with higher serum PTH (P=.04); and at a calcium intake of more than 1200 mg/d, there was a significant difference between the lowest and highest vitamin D groups (P=.04).

Conclusions As long as vitamin D status is ensured, calcium intake levels of more than 800 mg/d may be unnecessary for maintaining calcium metabolism. Vitamin D supplements are necessary for adequate vitamin D status in northern climates.

JAMA. 2005;294:2336-2341   www.jama.com

indicative of optimal calcium homeostasis and proposed as a marker of vitamin D sufficiency.[5,6] However, this approach to defining recommended vitamin D intake has been disputed, partly because there is considerable variation in the level of 25-hydroxyvitamin D associated with any given se-

Author Affiliations: Public Health Institute of Iceland (Dr Steingrimsdottir); University of Iceland (Drs Gunnarsson and Sigurdsson); and Department of Medicine (Drs Indridason and Sigurdsson) and Clinical Chemistry (Dr Franzson), Landspitali-University Hospital, Reykjavik, Iceland.
Corresponding Author: Gunnar Sigurdsson, MD, PhD, Division of Endocrinology and Metabolism, Department of Medicine, Landspitali-University Hospital, Fossvogur, IS-101 Reykjavik, Iceland (gunnars@landspitali.is).

rum PTH concentration, and reported threshold levels have varied greatly from 8 to 44 ng/dL.[7,8] This wide range may be in part due to different methods for measuring both serum PTH and 25-hydroxyvitamin D and defining baseline levels,[9] and possibly also due to different calcium intakes in study populations since serum calcium regulates PTH release.[10] The interrelationship between calcium intake and vitamin D requirements has not been addressed adequately in the past.

The goal of our study was to investigate the relative importance of high calcium intake and serum 25-hydroxyvitamin D for calcium homeostasis in healthy adults, as determined by serum intact PTH.

METHODS
Participants

A total of 2310 men and women were divided equally between 3 age groups (30-45 years, 50-65 years, and 70-85 years), identified by a stratified, random selection process from the computerized population register of Reykjavik, the capital of Iceland, and invited to participate in our cross-sectional study on bone health. In the preparatory phase of the study, we determined the sample size to have 80% power to detect a 20% difference in key bone factors between groups of 100 patients, at the $\alpha = .05$ significance level, presuming an SD of half the mean for the factor. With a 65% to 70% expected participation rate and after exclusions for various conditions, we predicted that the total of 2310 participants would be needed for invitation to the study. Women outnumbered men in the sample (n=1370 and n=940, respectively) because a greater proportion of women were expected to be excluded from the study due to hormonal use. The recruitment period was from February 2001 to January 2003, with an equal number of participants from each age group recruited monthly throughout the 2-year period to account for seasonal effects. The participants answered a detailed questionnaire on health-related issues, height and weight were measured, and body mass index (BMI)

was calculated as weight in kilograms divided by the square of height in meters. The Icelandic Medical Ethics Committee approved the study, and all participants provided a written consent form.

Dietary Assessment

Vitamin D and calcium intake were assessed by using a self-administered, semi-quantitative food frequency questionnaire, which was developed by the Icelandic Nutrition Council.[11] The questionnaire is designed to assess the entire diet, including supplements, over the previous 3-month period. It has been described and used in several studies and validated for foods and nutrients, including both calcium and vitamin D, and repeated 24-hour recalls were used as the reference method.[12] Vitamin D intake assessed by this method has also been validated using serum 25-hydroxyvitamin D as a biomarker in adult women not exposed to sunlamps in winter ($r=0.7$, $P<.001$).[13]

Biochemistry

After overnight fasting, blood was drawn between 8 and 10 AM, and serum 25-hydroxyvitamin D levels were measured using radioimmunoassay (DiaSorin, Stillwater, Minn). Interassay variations were 6.9% and 8.5% for serum 25-hydroxyvitamin D levels of 14.8 and 50.8 ng/dL, respectively. Intact serum PTH was measured using an immunoassay (ElectroChemiLuminscence Immuno Assay, Elecsys 2010, Roche Diagnostics, Tenzberg, Germany). Interassay variation was 2.9% for a serum PTH level of 68.0 pg/mL. Serum cystatin C was measured by an immunoturbidimetric assay (DakoCytomation, Copenhagen, Denmark), and serum ionized calcium was measured by an ion-specific electrode (ABL 700, Radiometer, Copenhagen, Denmark); coefficient of variation was 1.0% and 2.2% for serum ionized calcium levels of 4.12 and 6.40 mg/dL (1.03 and 1.60 mmol/L), respectively.

Data Analysis

We used analysis of variance (ANOVA) to compare the 3 age groups with re-

spect to continuous variables, applying the Bonferroni method to control for multiple comparisons. Two groups based on supplement use were compared using analysis of covariance (ANCOVA). Participants were divided into groups according to calcium intake (<800 mg/d, 800-1200 mg/d, and >1200 mg/d), and according to serum 25-hydroxyvitamin D level (<10 ng/mL, 10-18 ng/mL, and >18 ng/mL). Our main analysis by ANCOVA was to study the relationship between serum intact PTH levels and both calcium intake and serum 25-hydroxyvitamin D levels, with and without the interaction between calcium intake and vitamin D status in the model. Calcium intake groups and 25-hydroxyvitamin D groups were fixed factors, and variables known to be associated with PTH levels were entered as covariates, which included the continuous variables age, BMI, and cystatin C (as a measure of kidney function, independent of muscle mass and sex), and the categorical variables sex (male/female) and smoking (yes/no). We also tested for interaction between vitamin D status or calcium intake and the categorical variables smoking and sex, but these were not significant. For subsequent subgroup comparisons, we used Bonferroni adjustment for multiple comparisons. Groups were compared with regard to serum ionized calcium using ANOVA and the Bonferroni adjustment. Data are presented as mean (SD), unless otherwise noted. Statistical analysis was performed by using SPSS version 11.5 (SPSS Inc, Chicago, Ill). $P<.05$ was considered statistically significant.

RESULTS

A total of 1630 (70.7%) of 2310 individuals from the initial invited sample participated in the study; all were white. For our analysis, 625 participants were excluded because of diseases or medications thought to affect calcium metabolism, which included hormone therapy (n=304), thiazide diuretics (n=203), prednisolone (n=35), bisphosphonates (n=40), tamoxifen

Table. Mean Intake and Serum Values by Age Group

	Mean (SD) Values by Age Group, y			P Value*		
	30-45 (n = 358)	50-65 (n = 341)	70-85 (n = 245)	50-65 vs 30-45	70-85 vs 30-45	70-85 vs 50-65
Vitamin D intake, IU/d	388 (360)	552 (404)	664 (416)	<.001	<.001	.001
Calcium intake, mg/d	1175 (537)	1239 (552)	1308 (529)	.32	.007	.36
Serum 25-hydroxyvitamin D, ng/mL	17.1 (7.9)	18.3 (7.9)	20.7 (7.4)	.16	<.001	.001
Serum parathyroid hormone, pg/mL	35.8 (16.0)	37.7 (15.4)	41.7 (17.0)	.37	<.001	.01
Serum cystatin C, mg/L	0.9 (0.2)	1.0 (0.2)	1.2 (0.3)	<.001	<.001	<.001
Serum ionized calcium, mg/dL	4.92 (0.14)	4.95 (0.15)	4.97 (0.15)	.05	.002	.72

SI conversions: To convert serum 25-hydroxyvitamin to nmol/L, multiply by 2.496; serum ionized calcium to mmol/L, multiply by 0.25.
*Calculated by analysis of variance with Bonferroni adjustment.

Figure 1. Seasonal Variation in Serum 25-Hydroxyvitamin D by Supplemental Vitamin D Intake
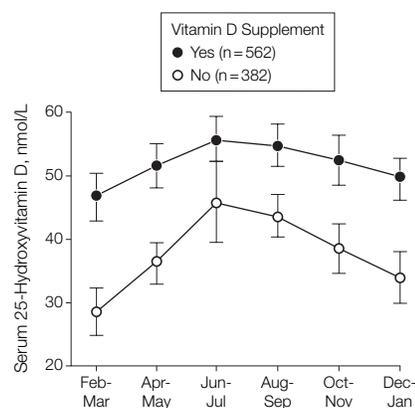
Data are presented as mean (SD). To convert serum 25-hydroxyvitamin D to ng/mL, divide by 2.496.

(n=18), phenytoin (n=5), major gastrointestinal surgery (n=28), and primary hyperparathyroidism (n=21); some participants were taking more than 1 medication. In addition, 61 participants were excluded because they failed to complete the dietary questionnaire. After all exclusions, 944 healthy participants remained who had completed all parts of the study (491 women; mean [SD] age, 53.7 [16.1] years; and 453 men; mean [SD] age, 57.9 [14.3] years).

Mean (SD) values for vitamin D and calcium intake, serum 25-hydroxyvitamin D, serum PTH, serum cystatin C, and serum ionized calcium in the 3 age groups are presented in the TABLE. All parameters were significantly higher in the oldest age group (70-85 years) compared with the youngest age group (30-45 years). Although mean intake of calcium and vitamin D were above recommended levels in all age groups, there was great variation in individual intake, especially for vitamin D.

FIGURE 1 presents mean serum 25-hydroxyvitamin D at 2-month intervals throughout the year for 2 groups (those participants taking vitamin D supplements or cod-liver oil regularly [n=562] and those not taking supplements [n=382]). Mean (SD) vitamin D intake levels were significantly higher in the group taking supplements compared with nonsupplement users (728 [372] vs 208 [200] IU/d; P<.001, ANOVA with no covariates; 1 µg corresponding to 40 IU of vitamin D), and was reflected in higher serum 25-hydroxyvitamin D levels, especially during the winter months, where mean (SD) levels decreased to 11.5 (5.5) ng/mL from February to March in those individuals not taking supplements but remained at 18.7 (8.1) ng/mL in the group taking supplements. Peak values during summer months, June to July, differed less between the groups but stayed nevertheless higher in supplement users at 22.4 (6.9) ng/mL compared with 18.3 (9.3) ng/mL in nonsupplement users. The difference in serum 25-hydroxyvitamin D levels between supplement and nonsupplement users was statistically significant (P<.001, ANCOVA controlling for season). In addition, serum PTH levels were significantly lower in supplement users compared with nonsupplement users (adjusted means, 36.9 vs 39.5 pg/mL; P=.02, ANCOVA controlling for age, sex, smoking, BMI, and cys-

tatin C). As expected, we found an inverse relationship between serum 25-hydroxyvitamin D and serum PTH levels; however, at serum 25-hydroxyvitamin D levels of more than 18 ng/mL, this relationship became statistically nonsignificant and only minor decrements in serum PTH levels were observed with serum 25-hydroxyvitamin D levels of more than 18 ng/mL. We therefore used a serum 25-hydroxyvitamin D level of 18 ng/mL to define vitamin D sufficiency.

In our main analysis, which examined factors in the model without the interaction term, vitamin D status was significantly associated with serum PTH (P<.001), whereas the calcium intake group was not (P=.28). In the model with the interaction term, both vitamin D status (P<.001), calcium intake group (P=.02), and the interaction between the 2 (P=.01) were significantly associated with serum PTH levels, as were all the covariates (all P≤.001). FIGURE 2 shows the adjusted means from the latter model for serum PTH according to serum 25-hydroxyvitamin D in the 3 calcium intake groups. The lowest serum PTH levels were observed in the group with a serum 25-hydroxyvitamin D level of more than 18 ng/mL, with a small difference between the calcium intake groups, whereas the highest serum PTH was observed in the group with a serum 25-hydroxyvitamin D level of less than 10 ng/mL. In this group, serum PTH levels were highest in the low calcium group. Thus, Figure 2 and the overall statistical model indicated a strong association between vitamin D status and serum PTH,

whereas the effect of calcium intake may be most important in the low vitamin D status group.

Further analysis of differences between subgroups was therefore limited to comparing the lower 2 calcium intake groups with the highest one within the lowest vitamin D status group, and the lower vitamin D status groups to the highest one within the highest calcium intake group. This was performed by using ANCOVA, adjusting for covariates and applying the Bonferroni method for multiple comparisons (total of 4 comparisons). At the low serum 25-hydroxyvitamin D level, there was a significant difference in serum PTH according to calcium intake. Serum PTH was significantly higher when the calcium intake level was less than 800 mg/d compared with more than 1200 mg/d (P=.04, ANCOVA with Bonferroni correction), whereas the serum PTH levels of those individuals with a calcium intake of between 800 and 1200 mg/d were not significantly different from those individuals with a level of more than 1200 mg/d. Within the highest calcium intake group, there was a significant difference between the lowest and the highest vitamin D groups (P=.04, ANCOVA with Bonferroni correction), whereas the difference between the middle and the highest groups was nonsignificant.

Mean serum ionized calcium was slightly but significantly lower in the group with the lowest serum 25-hydroxyvitamin D level compared with the highest group (4.908 vs 4.964 mg/dL [1.227 vs 1.241 mmol/L]; P = .01, ANOVA with Bonferroni adjustment for 6 comparisons). There was no significant difference in ionized calcium between the calcium intake groups, and the interaction between calcium intake and vitamin D sufficiency groups was not statistically significant. The lowest ionized calcium level was observed in the group with a serum 25-hydroxyvitamin D level of less than 10 ng/mL and calcium intake of less than 800 mg/d, or 4.72 mg/dL (1.18 mmol/L).

When all analyses above were performed on all 1630 participating indi-

viduals, including those excluded because of medications or diseases, similar results were obtained.

COMMENT

Our study examined calcium intake and serum levels of 25-hydroxyvitamin D with respect to optimal serum PTH. Parathyroid hormone is a major hormone maintaining normal serum concentrations of calcium and phosphate and is itself regulated through levels of calcitriol and serum calcium. An insufficiency of vitamin D or calcium is generally associated with an increase in PTH, but to our knowledge the relative importance of each nutrient to this process has not been addressed previously.

Our study was performed in a healthy adult population, living at a northern latitude (64° North), where sufficient sunshine for cholecalciferol biosynthesis is limited to the spring to autumn months. The study by Webb et al[14] demonstrated the effect of latitude on vitamin D biosynthesis, with no synthesis occurring due to sun exposure from December to February in Boston, Mass (42° North) and from November to March in Edmonton, Alberta, Canada (52° North). Our results point to a situation close to that in Edmonton, with serum 25-hydroxyvitamin D reaching its lowest values during the 2-month period from February to March. However, supplement use is common in this population, with 60% of our sample taking either cod-liver oil or vitamin D supplements regularly. The traditional use of cod-liver oil, which contains a high concentration of vitamin D, is especially common in older age groups in Iceland, accounting for higher mean intake levels in that age group.[13,15] Calcium intake is also relatively high in our sample, especially in older people, reflecting the common dietary pattern in Iceland and traditional use of milk products as verified in a recent national nutrition survey.[15] In spite of the high mean intake levels, there is considerable variation in both nutrients, allowing for the division of the sample into 3 groups of calcium in-

Figure 2. Adjusted Mean Serum Parathyroid Hormone Values According to Serum 25-Hydroxyvitamin D Values and Calcium Intake
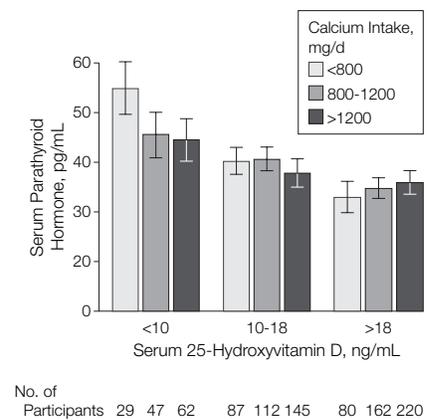
Data are presented as mean (SD). To convert serum 25-hydroxyvitamin D to nmol/L, multiply by 2.496.

take (<800 mg/d, 800-1200 mg/d, and >1200 mg/d), as well as 3 groups of serum 25-hydroxyvitamin D (<10 ng/mL, 10-18 ng/mL, and >18 ng/mL).

The significance of our study was demonstrated by the strong negative association between sufficient serum levels of 25-hydroxyvitamin D and PTH, with calcium intake varying from less than 800 mg/d to more than 1200 mg/d. Our results suggest that vitamin D sufficiency can ensure ideal serum PTH values even when the calcium intake level is less than 800 mg/d, while high calcium intake (>1200 mg/d) is not sufficient to maintain ideal serum PTH, as long as vitamin D status is insufficient. This is further reflected in ionized calcium levels that were dependent on serum 25-hydroxyvitamin D levels but not on calcium intake. High calcium intake does, however, ameliorate the increase in serum PTH that accompanies vitamin D insufficiency and does permit somewhat lower serum 25-hydroxyvitamin D levels for maintaining ideal serum PTH.

Although a cross-sectional study such as our study is not sufficient to demonstrate causality, the association between vitamin D status, calcium intake, and the interaction between these 2 with serum PTH levels is a strong in-

dication of the relative importance of these nutrients. However, intervention studies are needed to further address this issue.

A limitation of our study may be the use of a semi-quantitative food frequency questionnaire method for assessing nutrient intake; as such, this method can be of limited validity or accuracy. However, our method was specially designed to measure calcium and vitamin D intake and has been shown to be of good validity and accuracy for most major nutrients, including calcium and vitamin D, compared with repeated 24-hour recalls or by associating serum 25-hydroxyvitamin D with vitamin D intake during winter ($r=0.7$).[11-13]

Another limitation of our study is our single fasting measurement of serum PTH, which does not give an accurate portrayal of the calcium economy. Although a 24-hour integrated serum PTH would certainly be a better measure and manifesting the full effect of absorptive calcemia, such an effort is not feasible in a large study population. Similarly, our determination of serum 25-hydroxyvitamin D relied on a single measurement. In our study, serum PTH values seemed to level off at a serum 25-hydroxyvitamin D level of approximately 18 ng/mL, irrespective of calcium intake, and no statistically significant decrease was observed with increased serum 25-hydroxyvitamin D levels (>18 ng/mL). Different authors have reported different serum 25-hydroxyvitamin D levels for the inflection point of serum PTH and in some studies levels of more than 18 ng/mL are reported to be within the region of the curve.[6-8,16] It has even been reported that no such value may exist.[17] It is quite possible that serum PTH levels continue to decrease in response to serum 25-hydroxyvitamin D levels of more than 18 ng/mL; however, this was not evident from our study. Indeed, our study indicated that this curve may be dependent on calcium intake, which in turn may explain the differences observed between studies.

Although our data are based on a healthy subsample of the original random sample of the population, all analyses were also performed on the total group of participants, including those individuals with diseases or taking medications that affected calcium metabolism. Similar results were obtained from that larger group in all respects, demonstrating that a possibly distorted study group did not contribute to our results.

Our results are supported by the study of Kinyamu et al,[18] which showed that serum PTH concentration is inversely associated with calcium intake derived from vitamin D–fortified milk, but not calcium from other sources. It has also been postulated that high calcium intake may have a vitamin D–sparing effect, possibly through suppressed serum PTH and decreased 1,25-dihydroxyvitamin D. Similarly a low calcium intake has been proposed to aggravate vitamin D deficiency through increased catabolism of 25-hydroxyvitamin D.[19,20] The inverse hypothesis, however, that sufficient vitamin D may have a calcium-sparing effect has not to our knowledge been addressed previously.

Although the importance of preventing undue increases in serum PTH for bone health is generally recognized, evidence is lacking for identifying the exact levels that may be detrimental. However, secondary hyperparathyroidism is considered to play a significant role in the pathogenesis of age-related bone loss.[21,22] Also, it is well recognized that serum PTH is the principal systemic determinant of bone remodelling, which itself is a risk factor for fractures irrespective of bone balance.[23] Although sufficient intake of both nutrients is certainly important, our study indicates that as long as vitamin D status is secured by vitamin D supplements or sufficient sunshine, calcium intake levels of more than 800 mg/d may be unnecessary for maintaining calcium homeostasis. However, high calcium intake levels may have other beneficial effects not addressed in this study or reflected by serum PTH levels, including protective effects in the gut lumen against colon polyp formation.[24] It has been shown that large amounts of calcium are needed to meet body requirements in the absence of much active calcium transport in the gut, as in vitamin D insufficiency.[25] Our findings that serum PTH differs by calcium intake, only in those individuals with low vitamin D status, are most likely explained by less active transport of calcium.

In our sample population, an average intake of 500 IU/d of vitamin D corresponded with a mean serum 25-hydroxyvitamin D level of more than 18 ng/mL throughout the year but approximately 700 IU/d was required during winter. This is a comparable value with the levels recently recommended by several authors.[1-3] Although ideal intakes of these 2 nutrients need to be further defined in more elaborate studies, there is already sufficient evidence from numerous studies[1-3,6,16,17,26-28] for physicians and general practitioners to emphasize to a much greater extent the importance of vitamin D status and recommend vitamin D supplements for the general public, when sun exposure and dietary sources are insufficient.

In conclusion, our study suggests that vitamin D sufficiency may be more important than high calcium intake in maintaining desired values of serum PTH. Vitamin D may have a calcium-sparing effect and as long as vitamin D status is ensured, calcium intake levels of more than 800 mg/d may be unnecessary for maintaining calcium metabolism. Vitamin D supplements are necessary to ensure adequate vitamin D status for most of the year in northern climates.

REFERENCES

1. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr.* 2003;77:204-210.
2. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr.* 2004;79:717-726.
3. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr.* 2001;73: 288-294.
4. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev.* 2001;22:477-501.
5. Dawson-Hughes B, Harris SS, Dallal GE. Plasma calcidiol, season, and serum parathyroid hormone concentrations in healthy elderly men and women. *Am J Clin Nutr.* 1997;65:67-71.
6. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int.* 1997;7:439-443.
7. Report of the Subgroup on Bone Health; Working Group on the Nutritional Status of the Population of the Committee on Medical Aspects of the Food Nutrition Policy. Nutrition and bone health: with particular reference to calcium and vitamin D. *Rep Health Soc Subj (Lond).* 1998;49:1-24.
8. Bates CJ, Carter GD, Mishra GD, O'Shea D, Jones J, Prentice A. In a population study, can parathyroid hormone aid the definition of adequate vitamin D status? a study of people aged 65 years and over from the British National Diet and Nutrition Survey. *Osteoporos Int.* 2003;14:152-159.
9. Lips P, Chapuy MC, Dawson-Hughes B, Pols HA, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. *Osteoporos Int.* 1999;9:394-397.
10. Heaney RP. Ethnicity, bone status, and the calcium requirement. *Nutr Res.* 2002;22:153-178.
11. Thorsdottir I, Gunnarsdottir I, Steingrimsdottir L. Validity of a food frequency questionnaire to assess dietary intake of adults. *Laeknabladid (Icel Med J).* 2004;90:37-41.
12. Olafsdottir AS, Magnusardottir AR, Thorgeirsdottir H, Hauksson A, Skuladottir GV, Steingrimsdottir L. Relationship between dietary intake of cod-liver oil in early pregnancy and birthweight. *BJOG.* 2005;112: 424-429.
13. Sigurdsson G, Franzson L, Thorgeirsdottir H, Steingrimsdottir L. Vitamin D intake and serum 25-OH-vitamin D concentration in different age groups of Icelandic women. *Laeknabladid (Icel Med J).* 1999; 85:398-405.
14. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab.* 1988;67:373-378.
15. Steingrimsdottir L, Thorgeirsdottir H, Olafsdottir AS. *Icelandic National Nutrition Survey 2002.* Reykjavik, Iceland: Public Health Institute of Iceland; 2003.
16. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med.* 1998;338:777-783.
17. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ.* 2003;326:469-474.
18. Kinyamu HK, Gallagher JC, Rafferty KA, Balhorn KE. Dietary calcium and vitamin D intake in elderly women: effect on serum parathyroid hormone and vitamin D metabolites. *Am J Clin Nutr.* 1998;67:342-348.
19. Lips P. Does calcium intake change vitamin D requirements? In: Burckhart P, Dawson-Hughes B, Heaney RP, eds. *Nutritional Aspects of Osteoporosis: Serono Symposium.* New York, NY: Springer-Verlag; 1998:262-267.
20. Lips P, Netelenbos JC, van Doorn L, Hackeng WH, Lips CJ. Stimulation and suppression of intact parathyroid hormone (PTH1-84) in normal subjects and hyperparathyroid patients. *Clin Endocrinol (Oxf).* 1991;35:35-40.
21. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med.* 1992;327:1637-1642.
22. Sigurdsson G, Franzson L, Steingrimsdottir L, Sigvaldason H. The association between parathyroid hormone, vitamin D and bone mineral density in 70-year-old Icelandic women. *Osteoporos Int.* 2000;11: 1031-1035.
23. Heaney RP. Is the paradigm shifting? *Bone.* 2003; 33:457-465.
24. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med.* 1999;340:101-107.
25. Heaney RP. Vitamin D: role in the calcium economy. In: Feldman D, Pike JW, Glorioux FH, eds. *Vitamin D.* Amsterdam, the Netherlands: Elsevier Inc; 2005:773-787.
26. Ooms ME, Lips P, Roos JC, et al. Vitamin D status and sex hormone binding globulin: determinants of bone turnover and bone mineral density in elderly women. *J Bone Miner Res.* 1995;10:1177-1184.
27. Harkness L, Cromer B. Low levels of 25-hydroxy vitamin D are associated with elevated parathyroid hormone in healthy adolescent females. *Osteoporos Int.* 2005;16:109-113.
28. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr.* 2003;89:552-572.