

Age but not gender modulates the relationship between PTH and vitamin D

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ABSTRACT

Context: It is unclear whether the relationship between 25-OHD and PTH is modulated by age or gender. **Objective:** To assess the 25-OHD–PTH relationship in 340 adolescents (10–17 years) and 443 elderly (65–85 years) of the same ethnic group, and living in the same sunny country.

Assessments: Calcium intake was estimated. Serum calcium, phosphorus, 25-OHD and PTH were measured. Body fat was determined by DXA.

Results: 25-OHD levels were lower in the elderly in the overall group ($p < 0.001$) and within genders. 25-OHD levels were lower in females in the overall group and within age subgroups ($p < 0.05$). PTH levels were higher in the elderly in the overall population and in both genders ($p < 0.001$). There were no gender differences in PTH levels within age subgroups. For the same 25-OHD level, PTH levels were comparable across genders but were 1.5–2 folds higher in the elderly compared to adolescents ($p < 0.001$). PTH correlated positively with age ($p < 0.001$), body fat ($p = 0.02$), and negatively with calcium intake ($p < 0.001$), and 25-OHD ($p < 0.001$). The magnitude of the correlation with 25-OHD decreased after adjustment for age but not for gender. In multivariate analyses, age, 25-OHD and fat mass were independent predictors for PTH. In the elderly, after adjustment for serum creatinine, only 25-OHD and creatinine were independent predictors of PTH.

Conclusion: The negative relationship between 25-OHD and PTH is modulated by age but not gender. Desirable 25-OHD levels derived from examining the 25-OHD–PTH relationship should therefore take into account the age of the population of interest.

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Introduction

Hypovitaminosis D is a global problem, prevalent across genders and age groups, even in sunny countries [1]. Using cut-off values of 20 ng/ml to define deficiency and 30 ng/ml to define insufficiency, it is estimated that one billion individuals have vitamin D insufficiency or deficiency worldwide [2]. There is growing evidence that vitamin D sufficiency is required for optimal health in general, and musculoskeletal health in particular [2]. One of the primary roles of vitamin D is to regulate calcium and phosphorus metabolism and maintain adequate bone health [3].

Over the last few years, discussions have focused on determining desirable serum 25 (OH) vitamin D [25-OHD] levels to optimize bone health, using various surrogate markers of vitamin D status, including the relationship between serum 25-OHD and parathormone (PTH) levels [3,4].

The inverse relationship between serum 25-OHD and PTH levels has been well described but this relationship varied across studies and

populations. Some studies showed that a serum level between 50 and 80 nmol/l is needed to obtain maximal suppression of PTH, others have defined the level between 30 and 50 nmol/l [5]. In one study, serum PTH was inversely related to vitamin D in white but not in black adolescent American girls [6]. In a recent study, Hill et al. showed that in Irish girls, a plateau in PTH was observed at a 25-OHD concentration of 60 nmol/l whereas no plateau in PTH concentrations was observed in boys [7]. Thus ethnicity and gender may play a determinant role in this relationship, and, consequently in the difference observed between studies. Other confounders that may influence this relationship may include factors that affect vitamin D and/or PTH levels such as aging, BMI, calcium intake and absorption, sex steroid levels and kidney function [7–11]. An age-related rise in serum PTH by 25 to 30% has been reported between 20 and 85 years of age [9], probably due to an age-related decrease in calcium absorption [10] and decrease in kidney function. In one study, the age-related increase in serum PTH was eliminated with long term estrogen therapy in postmenopausal women [13].

Therefore, although the inverse relationship between PTH and vitamin D is well known, its modulation by age and gender has not been systematically investigated. The aim of the current study is to investigate the effect of age and gender on the 25-OHD/PTH relation within the same population.

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Materials and methods

Study participants

460 ambulatory, home-dwelling elderly, aged 65–85 years (73 ± 5.2) participated in a population-based study aiming at assessing the prevalence of osteoporosis and vertebral fractures in the Lebanese elderly [14]. 11 subjects (2 men and 9 women) were excluded from the analyses because of suspicion of primary hyperparathyroidism, based on a serum calcium ≥ 10.5 mg/dl and PTH levels above the upper limit of normal (76 pg/ml). Serum 25-OHD levels were missing in 6 subjects; thus, data from 443 subjects (286 women and 157 men) were included in the analyses.

In addition, baseline data from 340 children (172 boys and 168 girls) aged 10 to 17 years of age enrolled in a randomized, double-blind, placebo-controlled trial evaluating the efficacy of vitamin D supplementation on skeletal health in adolescents were used for the purposes of this study [15].

All subjects were studied within the same season, and those who suffered a medical condition or took medications known to affect bone metabolism were excluded.

Ethics

Both studies were approved by the Institutional Review Board of the American University of Beirut. Written informed consent was obtained from all the elderly participants, and written assent from all the children and written consent from one of their parents.

Assessments

Clinical assessment

In both groups, height (cm) and weight (kg) were measured and BMI (kg/m^2) was calculated. In adolescents, pubertal status was assessed using Tanner staging of pubic hair. Calcium intake (mg/day) was estimated using a questionnaire. The dietary questionnaire used for adolescents was derived from a validated version developed in our unit that demonstrated that 80% of calcium intake in adolescents was from dairy products [16]. In the elderly, dairy calcium intake was assessed using a food frequency questionnaire that evaluated the consumption of calcium enriched foods, mostly from dairy products.

Biochemical assessments

In both studies, serum calcium (Ca) and phosphorus (PO₄) and alkaline phosphatase (AlkP) were measured by standard calorimetric methods, using the Hitachi 912 analyzer (Mannheim, Germany). Serum 25-OHD (ng/ml) was measured by a competitive protein-binding assay (Diasorin Incstar, Diasorin, Saluggia, Italy). The reference range as reported in the kit was 10–60 ng/ml. The endocrine core laboratory in our institution is a participant in the international vitamin D external quality assurance Service, DEQAS (<http://www.deqas.org>). Serum PTH was measured by ELSA-PTH immunoradiometric assay (CisBio International, Gif-Sur-Yvette, Cedex, France). The normal range as reported in the kit was 8–78 pg/ml. The intra-assay and the inter-assay variability for 25-OHD and PTH measurements in our lab were below 10%.

Total body composition was measured by DXA using Hologic device (QDR 4500 A, Bedford, MA).

Statistical analyses

Numbers are expressed as mean \pm SD. Independent *t*-test was used to assess the difference in mean 25-OHD level and PTH level between genders and between age groups. The relationship between PTH and vitamin D levels and other continuous variables was assessed using Pearson's correlation. Partial correlations were then performed

to assess the effect of age, gender and other covariates on this relationship. Because serum creatinine was not measured at baseline, creatinine measured in 195 elderly subjects who came for follow-up at 4.4 years was also used in the adjusted analyses. Multivariate analyses were conducted using stepwise linear regression models to assess the relationship between PTH and 25-OHD after adjustment for other predictors of PTH such as age, gender, fat mass, calcium intake, and serum creatinine in the elderly.

Results

Table 1 shows the baseline characteristics of both populations. The mean age was 73.6 ± 5.1 years in the elderly and 12.9 ± 2.0 years in the adolescents. In the overall group, 46% of the adolescents were prepubertal (stages I and II) and 54% were in stages III to V. Estimated calcium intake was 310 ± 280 mg/day in the elderly and 714 ± 858 mg in the young ($p < 0.001$ for difference between groups). Female subjects consumed less calcium than male subjects ($p < 0.001$), in the overall population and within age groups. Among the study participants, only 17 elderly subjects and none of the adolescents were taking vitamin D supplements at baseline.

In the elderly, 65.8% of the women were wearing veil and 34.2% were not. In the young group, these percentages were 16.8% and 83.2% respectively.

Vitamin D levels by age and gender

Mean 25-OHD levels were lower in the elderly compared to adolescents. This was consistent in the overall group (11.4 ± 4.9 versus 15.3 ± 7.5 ng/dl, $p < 0.001$) and within gender subgroups, 12.1 ± 4.6 versus 16.5 ± 6.7 ng/dl in male and 10.9 ± 5.0 versus 14.2 ± 8.1 ng/dl in female subjects. Mean 25-OHD levels were lower in females compared to males (12.1 ± 6.5 versus 14.4 ± 6.1 ng/dl, $p < 0.05$ in the overall group, and within age subgroups, 10.9 ± 5 versus 12.1 ± 4 ng/dl in elderly and 14.2 ± 8 versus 16.5 ± 6 ng/dl in children, $p < 0.05$).

In women, 25-OHD levels were lower in veiled versus non-veiled group (9.1 ± 3.5 versus 11.7 ± 5.5 , $p < 0.001$ in the elderly and 7.3 ± 2.3 versus 15.4 ± 8.2 , $p < 0.001$ in the adolescents).

Vitamin D subgroups were created using the following 25-OHD cut-off levels: < 10 ng/ml, 10–20 ng/ml, 20–30 ng/ml and > 30 ng/ml (Table 2). Almost half the elderly and one fourth of the young had vitamin D levels below 10 ng/ml. Very few subjects (1% of the elderly and 5% of the young) had vitamin D above 30 ng/ml (Table 2). The proportion of subjects within the lowest vitamin D subgroups were higher in female than male subjects (Table 2).

PTH levels by age and gender

Mean PTH levels were higher in the elderly compared to adolescents (44.0 ± 47 versus 18.4 ± 20 pg/dl, $p < 0.001$). This was consistent in the overall population, and within gender subgroups. There were no gender differences in PTH levels in either age group.

Within each vitamin D level subgroup, mean PTH levels were comparable across genders (Fig. 1). Within each vitamin D level, mean 25-OHD levels were comparable across age groups, but PTH levels were 1.5–two folds higher in the elderly ($p < 0.001$, Fig. 2).

Relationships between vitamin D, PTH levels and other determinants

There was a negative correlation between 25-OHD and PTH in the overall group ($r = -0.25$, $p < 0.001$), within age groups ($r = -0.16$, $p = 0.005$ in the adolescents and $r = -0.20$, $p < 0.001$ in the elderly) and within genders ($r = -0.23$, $p < 0.001$, same values were found in both genders). 25-OHD correlated positively with calcium intake ($r = 0.22$, $p < 0.001$) and negatively with age ($r = -0.3$, $p < 0.001$), BMI ($r = -0.17$, $p < 0.001$) and with total body fat ($r = -0.13$, $p < 0.001$).

Table 1
Clinical and biochemical characteristics of the study population*.

	Overall elderly (N=443)	Overall young (N=340)	Overall male (N=329)	Overall female (N=454)	Elderly male (N=157)	Elderly female (N=286)	Young male (N=172)	Young female (N=168)
Age (years)	73.6 ± 5.1 ^a	12.9 ± 2.0 ^a	–	–	74.0 ± 5.0	73.4 ± 5.2	12.8 ± 1.9	13.0 ± 2.1
Calcium (mg/dl)	9.3 ± 0.5 ^a	9.9 ± 0.3 ^a	9.7 ± 0.5	9.6 ± 0.5	9.3 ± 0.4 ^c	9.4 ± 0.5 ^d	10.0 ± 0.3 ^c	9.9 ± 0.4 ^d
Phosphorus (mg/dl)	3.4 ± 0.5 ^a	4.4 ± 0.5 ^a	3.9 ± 0.9	3.9 ± 0.6	3.1 ± 0.5 ^c	3.6 ± 0.5 ^d	4.6 ± 0.5 ^c	4.3 ± 0.6 ^d
Alkaline phosphatase (IU/l)	88.3 ± 32.1 ^a	260 ± 120 ^a	203.1 ± 130 ^b	144.1 ± 107 ^b	82.5 ± 29 ^{c,e}	91.5 ± 33 ^{d,e}	296.1 ± 98 ^{c,f}	222.9 ± 129 ^{d,f}
Serum 25 vitamin D (ng/ml)	11.4 ± 4.9 ^a	15.3 ± 7.5 ^a	14.4 ± 6.1 ^b	12.1 ± 6.5 ^b	12.1 ± 4.6 ^{c,e}	10.9 ± 5.0 ^{d,e}	16.5 ± 6.7 ^{c,f}	14.2 ± 8.1 ^{d,f}
Serum PTH (pg/ml)	44.0 ± 47.1 ^a	18.4 ± 20.9 ^a	31.0 ± 37.7	35.0 ± 42.3	43.9 ± 48.0 ^c	44.1 ± 46.6 ^d	18.4 ± 15.6 ^c	18.4 ± 25.5 ^d
Calcium intake (mg/day)	310 ± 280 ^a	714 ± 358 ^a	581 ± 379 ^b	493 ± 365 ^b	354 ± 280 ^{c,e}	286 ± 277 ^{d,e}	756 ± 352 ^{c,f}	670 ± 359 ^{d,f}
Pubertal status								
Tanner I		21.2%					16.7%	25.6%
Tanner II		25.0%					16.7%	33.1%
Tanner III		12.6%					12.5%	12.8%
Tanner IV		20.9%					28.0%	14.0%
Tanner V		20.3%					26.2%	14.5%

*Values in the same row, with the same superscript, are significantly different from each other, $p < 0.05$.

PTH positively correlated with age ($r = 0.31$, $p < 0.001$), total body fat ($r = 0.10$, $p = 0.02$) and negatively with calcium intake ($r = -0.19$, $p < 0.001$). In the elderly, serum creatinine correlated with PTH ($r = 0.2$, $p = 0.01$) but not with 25-OHD.

Adjusted analyses

The magnitude of the negative correlation between PTH and 25-OHD decreased, although it remained significant after adjustment for age ($r = -0.25$ versus -0.17 , $p < 0.001$). The strength of this negative correlation did not change after adjustment for gender ($r = -0.24$, $p < 0.001$), BMI ($r = -0.23$, $p = 0.001$), body fat ($r = -0.24$, $p = 0.001$) and calcium intake ($r = -0.21$, $p < 0.001$).

In a multivariate model, 25-OHD, age and fat mass were significant independent predictors for serum PTH levels in the overall group: $\beta = 0.47$, $p < 0.001$ for age in years, $\beta = -0.95$, $p < 0.001$ for 25-OHD in ng/ml, and $\beta = -0.51$, p for total body fat in kg, $p = 0.04$. $R^2 = 14.6\%$. When the regression models were built for the young group and the elderly group separately, age and 25-OHD remained significant independent predictors for PTH level in the young group ($R^2 = 6.4\%$) whereas age, fat mass and 25-OHD remained significant independent predictors for PTH levels in the elderly ($R^2 = 6.2\%$).

In the elderly, after adjustment for serum creatinine, only 25-OHD and creatinine remained as independent predictors for PTH ($p = 0.01$ for creatinine, $p < 0.001$ for 25-OHD).

Discussion

25-OHD levels were lower in the elderly compared to young adolescents of the same ethnic group and living in the same sunny country. The vitamin D–PTH relationship varied by age but not

Table 2
Frequency distribution of the study population by 25-OHD level subgroup.

25-OHD level subgroups	Elderly ^a			Children ^b		
	Overall N = 443	Women N = 286	Men N = 157	Overall N = 340	Girls N = 168	Boys N = 172
0–10 ng/ml	217	159	58	81	57	24
	49%	56.3%	37.1%	23.8%	33.9%	14%
10–20 ng/ml	202	113	89	197	84	113
	45.2%	39%	56.6%	57.9%	50.0%	65.7%
20–30 ng/ml	19	10	9	44	18	26
	4.2%	3.4%	5.7%	12.9%	10.7%	15.1%
>30 ng/ml	5	4	1	18	9	9
	1.1%	1.4%	0.6%	5.3%	5.4%	5.2%

^a Significant difference in the distribution by 25-OHD level subgroup between genders by Fisher's Exact test, ($p = 0.001$).

^b Significant difference in the distribution by 25-OHD level subgroup between genders by chi-square ($p < 0.001$).

gender. For the same 25-OHD level subgroup, PTH levels were on the average two folds higher in the elderly compared to the young, but there was no difference in mean PTH levels between genders. The strength of the relationship between vitamin D and PTH decreased after adjustment for age but not gender.

Over 25 years ago, MacLaughlin and Holick reported that elderly subjects have lower 25-OHD levels than young adults because of diminished cutaneous production of vitamin D with aging [17]. The lower 25-OHD levels in our elderly may be due to a lower sun exposure, since elderly individuals in our country spend little time outdoors (unpublished observations). In both age groups, females had lower vitamin D levels compared to males. The age-related fall in vitamin D level is not the same in both genders and may occur at a younger age in women than men [18]. Although some studies have shown higher 25-OHD levels and lower PTH in men compared to women throughout the year [19,20], this finding was not consistent in

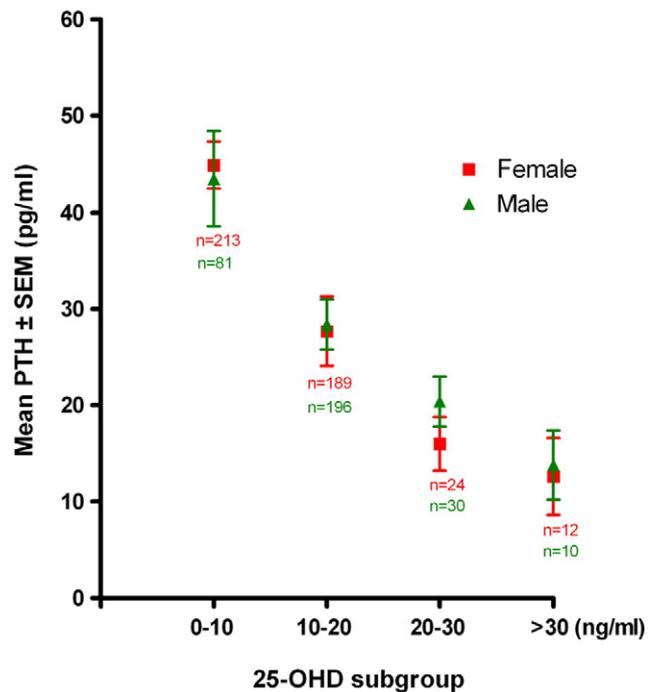


Fig. 1. Mean ± SD PTH values (pg/ml) across 25-OHD subgroups (0–10 ng/ml, 10–20 ng/ml, 20–30 ng/ml and >30 ng/ml) by gender. The mean 25-OHD levels in the above ascending subgroups were 7.7 ± 1.3 ng/ml, 13.6 ± 2.7 ng/ml, 23.6 ± 2.8 ng/ml and 37.8 ± 8.2 ng/ml in females and 8.2 ± 1.2 ng/ml, 14.3 ± 2.6, 23.4 ± 2.5 ng/ml and 36.4 ± 5.3 ng/ml in males. There was no difference in PTH levels between genders by 25-OHD subgroups.

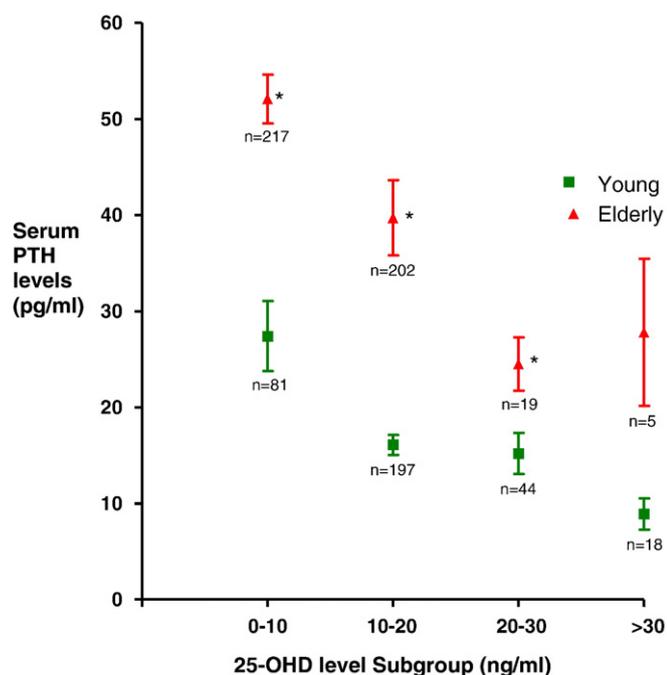


Fig. 2. Mean \pm SD PTH values (pg/ml) across 25-OHD subgroups (0–10 ng/ml, 10–20 ng/ml, 20–30 ng/ml and >30 ng/ml) by age group. The mean 25-OHD levels in the above ascending subgroups were 7.8 ± 1.5 ng/ml, 14.5 ± 2.7 , 23.7 ± 2.6 ng/ml, and 37.1 ± 6.9 ng/ml for the adolescents and 7.9 ± 1.3 ng/ml, 13.4 ± 2.5 ng/ml, 23.1 ± 2.6 ng/ml and 35.3 ± 3.0 ng/ml for the elderly. There was a significant difference in PTH levels between the young and the elderly by 25-OHD levels subgroups ($p < 0.001$).

all studies [21–23]. In our study, the lower levels of vitamin D in females mainly reflect life and dress style. In our community, elderly men spend more time outdoors than women [24] and boys play outdoors more than girls [16].

There was a negative correlation between 25-OHD and fat mass. Subjects with increased body weight have been reported to have a lower level of vitamin D than normal weight individuals, possibly due to increased sequestration of the vitamin into subcutaneous adipose tissue [25–30]. Kull et al. has recently suggested that this difference might in part be related to a difference in sunbathing habits between obese and lean subjects [31], but this was not confirmed in the elderly [32].

Serum PTH correlated with age and the levels were higher in the elderly than in young. This was expected in view of the lower calcium intake and levels of serum 25-OHD in the elderly. However, this relationship between PTH and age persisted after adjustment for 25-OHD in multivariate analyses, suggesting that PTH increases with age, independent of vitamin D status. This possibly reflects the decline in creatinine clearance with aging. Patel et al. showed that glomerular filtration rate is an important determinant of the serum PTH level for low levels of 25-OHD [12]. We did not measure creatinine in the young subgroup but in the subset of elderly where serum creatinine was obtained at follow-up, PTH correlated with creatinine level and the relationship between age and PTH disappeared after adjustment for creatinine suggesting that the effect of age on PTH is mediated by decline in kidney function.

PTH correlated also with BMI and total body fat and this relationship persisted after adjustment for vitamin D, in consistency with previous reports showing that fat mass is a determinant of serum PTH levels, independent of the inverse relationship between 25-OHD and fat mass [33–35].

The negative correlation between PTH and 25-OHD levels has been consistently described in many studies, with comparable correlation coefficients both in elderly and young individuals [7,36–40]. In our study we demonstrated that the strength of this relationship remained unchanged after adjustment for gender. Conversely, age

affected the relationship between 25-OHD and PTH. This is consistent with the findings of Vieth et al. [41] who, in a large cohort, showed that PTH levels of the elderly who had 25-OHD concentrations greater than 100 nmol/l matched PTH of younger adults having 25-OHD concentrations near 70 nmol/l. The strength of this correlation between PTH and 25-OHD was attenuated after adjustment for age ($r = -0.25$ versus $r = -0.17$). Moreover, for the same mean 25-OHD level, PTH levels were 1.5 times higher in the elderly compared to adolescents. The effect of age on the relationship between PTH and 25-OHD in the current study possibly reflects differences in calcium intake, calcium absorption, and kidney function between the two age groups. Indeed, calcium intake was lower in the elderly than in adolescents and PTH negatively correlated with calcium intake. A previous study demonstrated that high calcium intake ameliorates the increase in PTH that accompanies vitamin D insufficiency and permits lower vitamin D levels to maintain normal PTH levels, although it is not sufficient to maintain ideal serum PTH if vitamin D levels were not adequate [42]. Two recent studies evaluated the effect of age and calcium intake on the relationship between 25-OHD and PTH [8,40]. A large study including healthy adults aged 30–85 years showed a strong relationship between PTH and 25-OHD with an interaction between 25-OHD and calcium intake with PTH level so that an adequate vitamin D status can ensure ideal serum PTH values even when calcium intake is low and a high calcium intake can ensure normal PTH level if vitamin D status is inadequate [40]. Adami et al. in a cohort of elderly women with mean age 66 years, a mean 25-OHD level of 155 nmol/l and mean calcium intake of 507 mg showed that the relationship between 25-OHD and PTH was modulated by age and calcium intake [8]. In the current study, although calcium intake negatively correlated with PTH levels, it did not affect the strength of the negative correlation between 25-OHD and PTH, possibly because vitamin D levels and calcium intake were both low.

Our study demonstrates the major impact of age, but not gender, on the 25OHD–PTH relationship. PTH rather than 25-OHD level is the major modulator of bone mass [24], bone loss rates [43], and fractures [44] in adults. PTH appeared to play a role on bone health in children too. PTH was inversely related to BMD after adjustment for calcium intake, bone age and menarche in adolescent Italian girls [45]. Other studies in adolescents supported the importance of PTH not 25-OHD in modulating BMD when calcium intake is low or inadequate [46,47]. A higher PTH within the normal reference range appeared to be an indicator of bone mass accrual in this age group [46,47]. Thus the importance of taking age into consideration when defining desirable 25OHD levels, at least in the elderly and when bone metabolism is the outcome of interest. Whether this applies to non-classical effects of vitamin D is unclear.

Limitations of the study include its cross-sectional nature and the lack of availability of measurements of intestinal calcium absorption and renal function in the young age group, and at time of the study in the older age group. However, kidney function is not expected to be decreased in young healthy school children. Its advantage is the relatively large scope including individuals from the same ethnic background, of both genders, at extreme ends of the lifecycle, studied in the same period, and using the same PTH and 25-OHD assays in all subjects.

In Conclusion, age, BMI and total body fat mass are independent predictors of PTH levels in vitamin D deficient populations. For the same vitamin D level, PTH is on the average two folds higher in the elderly compared to adolescents. Desirable vitamin D levels derived from examining the 25-OHD–PTH relationship should take into consideration the age and kidney function of the target population.

Disclosures

All authors have made substantial contributions to the paper. The authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* 2009;20:1807–20.
- Holick M. Vitamin D deficiency. *N Engl J Med* 2009;19:266–81.
- Grant W, Holick M. Benefits and requirements of vitamin D for optimal health. *Altern Med Rev* 2005;10:94–111.
- Aloia JF, Talwar SA, Pollack S, Feuerman M, Yeh JK. Optimal vitamin D status and serum parathyroid hormone concentrations in African American women. *Am J Clin Nutr* 2006;84:602–9.
- Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005;16:713–6.
- Weaver CM, McCabe L, McCabe G, Braun M, Martin B, Dimeglio L. Vitamin D status and calcium metabolism in adolescent black and white girls on a range of controlled calcium intakes. *J Clin Endocrinol Metab* 2008;93:3907–14.
- Hill TR, Cotter AA, Mitchell S, Boreham CA, Dubitzky W, Murray L, et al. Vitamin D status and parathyroid hormone relationship in adolescents and its association with bone health parameters: analysis of the Northern Ireland Young Heart Project. *Osteoporos Int* 2010;21:695–700.
- Adami S, Viapiana O, Gatti D, Idolazzi L, Rossini M. Relationship between serum parathyroid hormone, vitamin D sufficiency, age, and calcium intake. *Bone* 2008;42:267–70.
- Quesada J, Coopmans W, Ruiz B, Aljama P, Jans I, Bouillon R. Influence of vitamin D on parathyroid functions in the elderly. *J Clin Endocrinol Metab* 1992;75:494–501.
- Nordin B, Need A, Morris H, O'Loughlin P, Horowitz M. Effect of age on calcium absorption in postmenopausal women. *Am J Clin Nutr* 2004;80:998–1002.
- Gunnarsson O, Idriidason OS, Franzon L, Sigurdsson G. Factors associated with elevated or blunted PTH response in vitamin D insufficient adults. *J Int Med* 2008;265:488–95.
- Patel S, Hyer S, Baron J. Glomerular filtration rate is a major determinant of the relationship between 25-hydroxyvitamin D and parathyroid hormone. *Calcif Tissue Int* 2007;80:221–6.
- Khosla S, Atkinson EJ, Melton III LJ, Riggs BL. Effects of age and estrogen status on serum parathyroid hormone levels and biochemical markers of bone turnover in women: a population-based study. *J Clin Endocrinol Metab* 1997;82:1522–7.
- Arabi A, Baddoura R, Awada H, Salamoun M, Ayoub G, El-Hajj Fuleihan G. Hypovitaminosis D osteopathy: is it mediated through PTH, lean mass, or is it a direct effect? *Bone* 2006;39:268–75.
- El-Hajj Fuleihan G, Nabulsi M, Tamim H, Maalouf J, Salamoun M, Khalife H, et al. Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial. *J Clin Endocrinol Metab* 2006;91:405–12.
- Salamoun M, Kizirian A, Tannous R, Nabulsi M, Choucair M, Deed M, et al. Low calcium and vitamin D intake in healthy children and adolescents and their correlates. *Eur J Clin Nutr* 2005;59:177–84.
- MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest* 1985;76:1536–8.
- Maggio D, Cherubini A, Lauretani F, Russo RC, Bartali B, Pierandrei M, et al. 25(OH)D serum levels decline with age earlier in women than in men and less efficiently prevent compensatory hyperparathyroidism in older adults. *J Gerontol A Biol Sci Med Sci* 2005;60:1414–9.
- Carnevale V, Modoni S, Pileri M, Di Giorgio A, Chiodini I, Minisola S, et al. Longitudinal evaluation of vitamin D status in healthy subjects from southern Italy: seasonal and gender differences. *Osteoporos Int* 2001;12:1026–30.
- Atli T, Gullu S, Uysal AR, Erdogan G. The prevalence of Vitamin D deficiency and effects of ultraviolet light on Vitamin D levels in elderly Turkish population. *Arch Gerontol Geriatr* 2005;40:53–60.
- Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003;78:1463–70.
- Lamberg-Allardt CJ, Outila TA, Kärkkäinen MU, Rita HJ, Valsta LM. Vitamin D deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe? *J Bone Miner Res* 2001;16:2066–73.
- Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, et al. Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. *Osteoporos Int* 2009;20:133–40.
- Arabi A, Baddoura R, Awada H, Salamoun M, Ayoub G, El-Hajj Fuleihan G. Hypovitaminosis D osteopathy: is it mediated through PTH, lean mass, or is it a direct effect? *Bone* 2006;39:268–75.
- Bolland MJ, Grey AB, Ames RW, Horne AM, Gamble GD, Reid IR. Fat mass is an important predictor of parathyroid hormone levels in postmenopausal women. *Bone* 2006;38:317–521.
- Benjamin A, Moriakova A, Akhter N, Rao D, Xie H, Kukreja S, et al. Determinants of 25-hydroxyvitamin D levels in African-American and Caucasian male veterans. *Osteoporos Int* 2009;20:1795–803.
- Lagunova Z, Porojnicu AC, Lindberg F, Hexeberg S, Moan J. The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Res* 2009;29:3713–20.
- Li J, Byrne ME, Chang E, Jiang Y, Donkin SS, Buhman KK, et al. 1 α , 25-Dihydroxyvitamin D hydroxylase in adipocytes. *J Steroid Biochem Mol Biol* 2008;112:122–6.
- Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. *J Clin Endocrinol Metab* 2005;90:4119–23.
- Valiña-Tóth AL, Lai Z, Yoo W, Abou-Samra A, Gadegbeku CA, Flack JM. Relationship of vitamin D and parathyroid hormone to obesity and body composition in African Americans. *Clin Endocrinol (Oxf)* 2010;72:595–603.
- Kull M, Kallikorm R, Lember L. Body mass index determines sunbathing habits: implications on vitamin D levels. *Int Med J* 2009;39:256–8.
- Harris S, Dawson-Hughes B. Reduced sun exposure does not explain the inverse association of 25-hydroxyvitamin D with percent body fat in older adults. *J Clin Endocrinol Metab* 2007;92:3155–7.
- Young KA, Engelman CD, Langefeld CD, Hairston KG, Haffner SM, Bryer-Ash M, et al. Association of plasma vitamin D levels with adiposity in Hispanic and African Americans. *J Clin Endocrinol Metab* 2009;94:3306–13.
- Grey AB, Evans MC, Stapleton JP, Reid IR. Body weight and bone mineral density in postmenopausal women with primary hyperparathyroidism. *Ann Intern Med* 1994;121:745–9.
- Reis JP, van Muihlen D, Kritiz-Silverstein D, Wingard DL, Barrett-Connor E. Vitamin D, parathyroid hormone levels and the metabolic syndrome in community-dwelling older adults. *Diab Care* 2007;30:1549–55.
- Haarburger D, Hoffman M, Erasmus RT, Pillay TS. Relationship between vitamin D, calcium and parathyroid hormone in Cape Town. *J Clin Pathol* 2009;62:567–9.
- Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P. Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. *J Clin Endocrinol Metab* 2009;94:1244–50.
- Yan L, Zhou B, Wang X, D'Ath S, Laidlaw A, Laskey MA, et al. Older people in China and the United Kingdom differ in the relationships among parathyroid hormone, vitamin D, and bone mineral status. *Bone* 2003;33:620–7.
- Abrams SA, Griffin IJ, Hawthorne KM, Gunn SK, Gundberg CM, Carpenter TO. Relationships among vitamin D levels, parathyroid hormone, and calcium absorption in young adolescents. *J Clin Endocrinol Metab* 2005;90:5576–81.
- El-Hajj Fuleihan G, Nabulsi M, Choucair M, Salamoun M, Hajj Shahine C, Kizirian A, et al. Hypovitaminosis D in healthy schoolchildren. *Pediatrics* 2001;107:E53.
- Steingrimsdottir L, Gunnarsson O, Idriidason O, Franzon L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. *JAMA* 2005;294:2336–41.
- Vieth R, Ladak Y, Walfish PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab* 2003;88:185–91.
- Arabi A, Baddoura R, El-Hajj Fuleihan G. PTH and not vitamin D predicts age-related bone loss in the elderly: a prospective population based study [Abstract]. *J Bone Miner Res* 23 (Suppl 1), M179.
- Rejnmark P, Vestergaard L, Mosekilde L. Parathyroid hormone level in vitamin D-replete postmenopausal women is an important predictor of fracture risk: a 16-yr follow-up study in postmenopausal women [Abstract]. *J Bone Miner Res* 2008;24 (Suppl 1) available at <http://www.asbmr.org/Meetings/AnnualMeeting/Abstracts09.aspx>, accessed February 8, 2010.
- Bonfiglio D, Maggiolini M, Catalano S, Marsico S, Aquila S, Andò S. Bone mineral density is inversely related to parathyroid hormone in adolescent girls. *Horm Metab Res* 2001;33:170–4.
- Bonfiglio D, Maggiolini M, Catalano S, Marsico S, Aquila S, Andò S. Parathyroid hormone is elevated but bone markers and density are normal in young female subjects who consume inadequate dietary calcium. *Br J Nutr* 2000;84:111–6.
- Tylavsky F, Ryder K, Li R, Park V, Womack C, Norwood J, et al. Preliminary findings: 25(OH)D levels and PTH are indicators of rapid bone accrual in pubertal children. *J Am Coll Nutr* 2007;26:462–70.