Effect of menopause and renal function on vitamin D status in Iranian women

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تأثير الإياس ووظيفة الكُلى على حالة الفيتامين D في النساء الإيرانيات

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الخلاصة: درس الباحثون تأثيرات الإياس ووظيفة الكُلَى على المتثابتات المصلية التي تعبِّر عن العلاقة بين الفيتامين D وبين جهاز الغدد الصم، وذلك في عينة مستعرضة من 676 امرأة موفورة الصحة في الفئة العمرية 20 — 74 عاماً، في مدينة شيراز. وبيَّنت الدراسة انخفاض الـ 25 – هيدروكسي فيتامين D في المصل في 52.9٪ من النساء. ولوحظ ازدياد ملموس في هرمون الدُّرَيْقَات في المصل مع تقدُّم عمر النساء في الفترة السابقة للإياس (معامل الترابط r = 0.13، P = 0.02). أما النساء في الفترة السابقة للإياس والفترة التالية للإياس، فكان مستوى الـ 25 – هيدروكسي فيتامين D في المصل والفوسفور، والكالسيوم ثابتاً مع تقدُّم العمر. و لم يُلاحَظ ترابط يُعْتَدُّ به إحصائياً بين تصفية الكرياتينين أو الهرمون الدريقي في المصل (معامل الترابُط = – 0.016 r، P = 0.66) وبين مستوى الـ 25 – هيدروكسي فيتامين D في المصل (معامل الترابُط = 0.012 r، P = 0.74). وهذا الانتشار المرتفع لعَوَز الفيتامين D يدعو إلى التفكير في إعطاء مكملات غذائية.

ABSTRACT The effects of menopause and renal function on serum parameters of the vitamin D-endocrine system were studied in a cross-sectional sample of 676 healthy women aged 20–74 years in Shiraz. Low serum 25-hydroxyvitamin D (25-OHD) was found in 52.9% of the women. Serum parathyroid hormone (PTH) increased significantly over the age span in premenopausal women ($r = 0.13$, $P = 0.02$). In premenopausal and postmenopausal women, serum levels of 25-OHD, phosphorus and calcium were stable across the age span. There was no significant correlation between creatinine clearance or serum PTH ($r = –0.016$, $P = 0.66$) and 25-OHD ($r = 0.012$, $P = 0.74$). The high prevalence of vitamin D deficiency warrants consideration of dietary supplementation.

Effet de la ménopause et de la fonction rénale sur le statut en vitamine D chez des femmes iraniennes

RÉSUMÉ Les effets de la ménopause et de la fonction rénale sur les paramètres sériques du système endocrinien de la vitamine D ont été étudiés dans un échantillon transversal de 676 femmes en bonne santé âgées de 20-74 ans à Chiraz. On a constaté une faible concentration sérique en 25-hydroxyvitamine D (25-OHD) chez 52,9 % des femmes. Le taux d'hormone parathyroïde (PTH) dans le sang augmentait de manière significative avec l'âge chez les femmes préménopausées (r = 0,13, p = 0,02). Chez les femmes préménopausées et postménopausées, la concentration sérique en 25-OHD, en phosphore et en calcium était stable dans la fourchette d'âge. Il n'y avait aucune corrélation significative entre la clairance de la créatinine ou la PTH sérique (r = - 0,016, p = 0,66) et la 25-OHD (r = 0,012, p = 0,74). La forte prévalence de la carence en vitamine D justifie la prise en compte d'une supplémentation alimentaire.

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Introduction

Vitamin D metabolites and parathyroid hormone (PTH) participate in the regulation of calcium homeostasis and bone metabolism. It is well known that vitamin D deficiency causes rickets in children and osteomalacia in adults [*1*]. It is believed that compromises in vitamin D status and/or a reduced capability of the kidney to synthesize 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] are responsible for impairment in dietary calcium absorption. These deficits lead to compensatory hypersecretion of parathyroid hormone, which results in bone loss [*2,3*]. The serum level of 25-hydroxyvitamin D (25-OHD) has been accepted as an index for vitamin D status [*4*].

Ruker et al. reported an inverse relationship between 25-OHD and body mass index (BMI) [*1*]. In addition, they found that PTH increased with increasing BMI.

Few investigators have examined the relationship of vitamin D status to key parameters of bone mineral homeostasis in healthy subjects in our country [*5*]. In addition, there is no consensus concerning the relationship of age to serum calcium, phosphorus and PTH levels. Knowledge of these relationships is vital to understanding changes in the levels of the bone mineral-regulating hormones and other related homeostatic variations.

The objective of this study, therefore, was to determine the relationship between age, renal function (serum creatinine and estimated creatinine clearance) and BMI and parameters of the vitamin D-endocrine system in healthy women.

Methods

Participants

The study was carried out from January to March 2001. Women aged 20–74 years were selected by cluster randomized sampling. The Shiraz city map was divided into 40 areas. In each area, homes whose postal code ended in 0 were selected. These addresses were visited and 1 woman from each was invited to participate in the study. The exclusion criteria were: history of fracture or metabolic bone disease; any malignancy at any age; history of thyroid, parathyroid or adrenal disease; history of drug abuse or alcoholism; any hepatic or renal disease; use of drugs which may affect bone and calcium metabolism, including estrogen, calcium, vitamin D supplements and anticonvulsant medication; oophorectomy; and gastrointestinal resection; 34 women did not meet these criteria.

The women were asked to come in a fasting state to the Endocrine and Metabolism Research Centre in Nemazi Hospital in the centre of Shiraz. We invited 880 women to participate and 710 came for the assessment (170 women refused to participate), a response rate of 80.7%. Of the 710 women, 36 were excluded leaving a final sample of 676 women. After informed consent was obtained, history was taken, blood samples were collected and a physical examination (thyroid, heart, lung, abdomen plus height and weight) carried out.

Biochemical tests

All blood samples were obtained from the women under fasting conditions between 08.00 and 10.00. The sera were stored at –20 °C until analysis was done in the laboratory of the Endocrine and Metabolism Research Centre.

Serum calcium (mg/dL; reference range 8.6–10.3 mg/dL), phosphorus (mg/dL; reference range 2.6–4.5 mg/dL), alkaline phosphatase (IU/L; reference range < 211 IU/L) and creatinine (mg/dL; reference range 0.6–1.1 mg/dL) were measured with enzyme kits (Pars Azmun, Tehran) and

a Hitachi 902 autoanalyser (Boehringer Mannheim, Mannheim, Germany). Serum albumin (g/dL; reference range 3.4–4.7 mg/dL) was measured by turbidimetric assay using a specific antibody.

Serum 25-OHD (reference range 23.1–113.0 nmol/L) level was measured using immunoradiometric assay with the IDS gamma-B 25-hydroxyvitamin D kit (IDS, Fountain Hills, Arizona). Serum intact parathyroid hormone (PTH pg/mL; normal range 13–54 pg/mL) was quantified using the immunoradiometric assay (DiaSorin, Stillwater, Minnesota).

Creatinine clearance was estimated by the Cockcroft and Gault formula [*6*], which takes serum creatinine (mg/dL), weight (kg), age (years) and sex into account: creatinine clearance (mL/min) = [(140 – age) × weight]/[72 × serum creatinine] × 0.85 (for women).

Height and weight were measured with a stadiometer and balance scale after participants had removed their shoes. All measurements were done on the same equipment. Body mass index was calculated as weight divided by the square of height (kg/m^2).

Statistical analysis

Data were presented as mean and standard deviation (SD). Pearson and partial correlation coefficients were used to determine the association among variables. Mean values were compared by student *t*-test. Statistical analyses were performed using *SPSS*, version 9.0. *P*-value < 0.05 (2-sided test) was considered statistically significant.

Results

The mean age of the participants in the study was 42.3 years (SD 13.4). Of the total of 676 women, 183 were postmenopausal, mean age 56.7 years (SD 8.6). Mean anthropometrical and biochemical measurements of participants are shown in Table 1.

25-hydroxyvitamin D

There was no relationship between age or body mass index and 25-OHD levels in the participants (premenopausal or postmenopausal) (Table 2). There was no statistically significant difference between the mean values for 25-OHD in premenopausal women and postmenopausal women ($P = 0.93$) (Table 1). We found 53.9% of premenopausal and 51.4% of postmenopausal women in the study had low levels of 25-OHD (≤ 23 nmol/L).

Parathyroid hormone

Mean serum PTH concentration was 33.1 pg/mL (SD 18.4) in premenopausal women and 34.5 pg/mL (SD 20.0) in postmenopausal women ($P = 0.42$) (Table 1). There was a statistically significant inverse relationship between serum PTH and 25-OHD ($r = –0.10$, $P = 0.009$) (Table 2). This relationship was independent of age ($r = –0.08$, $P = 0.047$).

Serum calcium and phosphorus

Total serum calcium was stable across the age span, mean 9.7 mg/dL (SD 0.8). In both the premenopausal and postmenopausal groups, the level of serum phosphorus was stable across the age span, $r = –0.005$, $P = 0.9$ and $r = 0.06$, $P = 0.37$ respectively (Table 2).

Alkaline phosphatase activity

Serum alkaline phosphatase was significantly correlated with age in the women we studied ($r = 0.23$, $P < 0.01$) (Table 2). Serum alkaline phosphatase level was significantly correlated with serum PTH and phosphorus in premenopausal ($r = 0.2$, $P = 0.01$ and $r = 0.14$, $P = 0.001$) and postmenopausal

Table 1 **Anthropometrical and biochemical of participants**

Parameter	Premenopause *n* = 493 Mean (SD)	Postmenopause *n* = 183 Mean (SD)	Total *n* = 676 Mean (SD)	*P*-value
Age (years)	34.4 (8.3)	56.7 (8.6)	42.3 (13.4)	0.0001
BMI (kg/m^2)	26.7 (2.6)	26.7 (1.6)	26.4 (1.9)	0.66
25-OHD (nmol/L)	28.9 (23.9)	29.1 (20.0)	28.9 (23.0)	0.93
PTH (pg/mL)	33.1 (18.4)	34.5 (20.0)	33.5 (19.1)	0.42
Calcium (mg/dL)	9.6 (0.8)	9.7 (0.6)	9.6 (0.8)	0.21
Phosphorus (mg/dL)	3.4 (0.5)	3.5 (0.5)	3.4 (0.5)	0.34
ALP (IU/L)	174.7 (78.3)	209.6 (65.3)	184.0 (70.6)	0.0001
Albumin (g/dL)	4.6 (0.4)	4.5 (0.3)	4.6 (0.4)	0.26
Cr (mg/dL)	1.1 (0.4)	1.2 (0.4)	1.1 (0.3)	0.02
Cl_{cr} (mL/min)	73.5 (10.0)	66.3 (8.0)	72.5 (9.9)	0.001

Serum values were determined and creatinine clearance estimated.
SD = standard deviation.
BMI = body mass index; 25-OHD = 25-hydroxyvitamin D; PTH = parathyroid hormone; ALP = alkaline phosphatase; Alb = Albumin; Cr = creatinine; Cl_{cr} = creatinine clearance.

women ($r = 0.2$, $P = 0.004$ and $r = 0.19$, $P = 0.007$) (Table 2). The serum alkaline phosphatase level was significantly higher in postmenopausal women, 209.6 IU/L (SD 65.3), than in premenopausal women, 174.7 IU/L (SD 70.3), ($P < 0.0001$) (Table 1).

Creatinine clearance

There was a significant decline in creatinine clearance with age ($r = –0.13$, $P = 0.001$). There was no significant correlation between serum PTH ($r = –0.016$, $P = 0.66$) or 25-OHD ($r = 0.012$, $P = 0.74$) and creatinine clearance.

Discussion

The most important finding in our study was the high rate (53.9% of premenopausal and 51.4% of postmenopausal women) of vitamin D deficiency in the participants. Lower rates of vitamin D deficiency have been reported in Iranian postmenopausal women (36%) and the general Saudi Arabian population (35%) [*5,7,8*]. But in North America, owing to oral vitamin D intake, hypovitaminosis D is rarely, if ever, reported in healthy young adults [*9–11*]. In Scandinavian countries, vitamin D deficiency has been reported in about 4%–9% of young adults during winter, and in up to 5% during summer [*12,13*].

Diet and sunlight are 2 sources of vitamin D in humans. Individuals in Iran have a limited intake of milk, and milk in Iran is generally not enriched with vitamin D. On the other hand, Shiraz is located in a subtropical area (latitude 29° N) and has abundant bright sunshine. So a low rate of hypovitaminosis D was expected in our general population. However, the extent of solar-ultraviolet (UV) exposure is determined primarily by lifestyle rather than ambient UV irradiation. The type of clothing used outdoors and the shorter amount of time spent outdoors are the most probable causes of greater hypovitaminosis D in women than expected. El-Sonbaty and

Table 2 **Correlation coefficients of biochemical variables with age, body mass index and with each other**

Parameter	Correlation coefficient							
	Age	BMI[a]	25-OHD	PTH	Ca	P	ALP	Cl_{cr}
25-OHD (nmol/L)								
Premenopause	0.06	0.01	–					
Postmenopause	0.04	0.14	–					
Total	0.05	0.04	–					
PTH (pg/mL)								
Premenopause	0.13**	0.03	–0.07	–				
Postmenopause	–0.08	–0.13	–0.17*	–				
Total	0.09*	0.01	–0.10**	–				
Ca (mg/dL)								
Premenopause	0.01	0.02	0.01	0.05	–			
Postmenopause	0.07	0.12	0.07	–0.03	–			
Total	0.05	0.04	0.03	0.03	–			
P (mg/dL)								
Premenopause	–0.01	–0.01	0.00	–0.01	0.31**	–		
Postmenopause	0.06	0.02	0.15*	–0.11	0.34**	–		
Total	0.03	–0.01	0.04	–0.04	0.32**	–		
ALP (IU/L)								
Premenopause	0.12**	0.05	–0.01	0.2**	0.15**	0.14**	–	
Postmenopause	0.11	–0.15*	–0.07	0.2**	0.19**	0.19**	–	
Total	0.23**	0.04	–0.03	0.20**	0.16**	0.16**	–	
Cl_{cr} (mL/min)								
Premenopause	–0.07	0.14**	0.01	0.011	–0.01	–0.02	–0.01	–
Postmenopause	–0.02	0.04	0.001	–0.08	0.13	0.09	–0.02	–
Total	–0.13**	0.12**	0.01	–0.02	0.01	0.01	–0.04	–
Alb (g/dL)								
Premenopause	–0.12**	–0.01	–0.02	0.01	0.35**	0.15**	0.09*	–
Postmenopause	–0.17*	–0.02	0.1	–0.14	0.23**	0.05	0.10	–
Total	–0.13**	–0.00	–0.01	–0.02	0.33**	0.13**	0.08*	–

Serum values were determined and creatinine clearance estimated.
Premenopause, n = 493; postmenopause, n = 183.
BMI = body mass index; 25-OHD = 25-hydroxyvitamin D; PTH = parathyroid hormone; Ca = calcium; P = phosphorus; ALP = alkaline phosphatase; Cl_{cr} = creatinine clearance; Alb = albumin.
**Correlation significant (P < 0.05).*
***Correlation significant (P < 0.01).*
[a]*Age-adjusted.*

Abdul-Ghaffar reported a similar finding in veiled Kuwaiti women [*14*].

Low level of serum 25-OHD, with normal calcium concentration and absence of osteomalacia necessitate the measurement of the active form of vitamin D, $1,25\text{-}(OH)_2D$, for reliable interpretation of the results [*15,16*]. This was a limitation of our study.

The absence of a decline in 25-OHD levels with age in our sample does not support the belief that a compromise in either

vitamin D status or the hormonal form of the vitamin is a normal concomitant of the ageing process [*17,18*].

The age-related increase in serum PTH in this study, similar to that found in other studies [*1,19,20*], cannot be attributed to an age-related decline in vitamin D status because serum 25-OHD levels were stable with age. However, the inverse relationship of serum PTH with serum 25-OHD, which is independent of age, suggests that vitamin D status may be a potentially important determinant of serum PTH levels. It has been hypothesized that elevated serum 25-OHD levels may decrease serum PTH secretion via direct interaction with 1,25-$(OH)_2$D receptors in the intestine to enhance calcium absorption and thereby normalize serum calcium levels and/or in the parathyroid gland to produce feedback inhibition of PTH secretion [*21*].

The absence of a correlation between serum PTH and creatinine clearance in the women we studied ($r = -0.01$, $P = 0.6$) does not corroborate the view that declining renal function is the primary mechanism responsible for the age-related increase in intact PTH [*19*]. It is likely that deficits in glomerular filtration rates substantially greater than those observed in our healthy participants may be necessary to produce the strong relationship between creatinine clearance and PTH observed by others [*22*].

We found relatively stable levels of total serum calcium and phosphorus in postmenopausal women. Some studies show no decline in total serum calcium [*23,24*] while others show a fall [*18,25*]. Reports concerning the effect of age on serum phosphorus level in women are also contradictory [*25,26*]. In both the premenopausal and the postmenopausal women in our study, serum phosphorus levels were constant with increasing age: this is not compatible with age-related increase in serum PTH.

Serum alkaline phosphatase activity rose with age in the women we studied; this is similar to the findings of Marcus, Madvig and Young [*19*] and Villareal et al. [*27*]. The serum alkaline phosphatase level was significantly higher in postmenopausal women, most probably as a result of hormonal changes during menopause which increases the effect of PTH on bone. On the other hand, there was a significant correlation between serum PTH and alkaline phosphatase level.

We conclude that in our healthy premenopausal or postmenopausal Iranian women, the prevalence of vitamin D deficiency is high, warranting consideration of dietary vitamin D supplementation.

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References

1. Rucker D et al. Vitamin D insufficiency in a population of healthy western Canadians. *Canadian Medical Association journal*, 2002, 166(12):1517–24.

2. Gallagher JC et al. Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients: effect of age and dietary calcium.

Journal of clinical investigation, 1979, 64(3):729–36.

3. Riggs BL, Melton LJ 3rd. Involutional osteoporosis. *New England journal of medicine*, 1986, 314(26):1676–86.
4. Schmidt-Gayk H, Bouillon R, Roth HJ. Measurement of vitamin D and its metabolites (calcidiol and calcitriol) and their clinical significance. *Scandinavian journal of clinical and laboratory investigation. Supplementum*, 1997, 227:35–45.
5. Rassouli A, Milanian I, Moslemi-Zadeh M. Determination of serum 25-hydroxy vitamin D3 levels in early postmenopausal Iranian women: relationship with bone mineral density. *Bone*, 2001, 29(5): 428–30.
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*, 1976, 16(1):31–41.
7. Sedrani SH. Vitamin D status of Saudi men. *Tropical and geographical medicine*, 1984, 36(2):181–7.
8. Sedrani SH, Elidrissy AW, El Arabi KM. Sunlight and vitamin D status in normal Saudi subjects. *American journal of clinical nutrition*, 1983, 38(1):129–32.
9. Haddad JG Jr, Hahn TJ. Natural and synthetic sources of circulating 25-hydroxy vitamin D in man. *Nature*, 1973, 244(5417):515–7.
10. Stryd RP, Gilbertson TJ, Brunden MN. A seasonal variation study of 25-hydroxy vitamin D3 serum levels in normal humans. *Journal of clinical endocrinology and metabolism*, 1979, 48(5):771–5.
11. Chesney RW et al. Absence of seasonal variation in serum concentrations of 1,25-dihydroxyvitamin D despite a rise in 25-hydroxyvitamin D in summer. *Journal of clinical endocrinology and metabolism*, 1981, 53(1):139–42.
12. Lund B, Sorensen OH. Measurement of 25-hydroxyvitamin D in serum and its relation to sunshine, age and vitamin D intake in the Danish population. *Scandinavian journal of clinical and laboratory investigation*, 1979, 39(1):23–30.
13. Vik T, Try K, Stromme JH. The vitamin D status of man at 70 degrees north. *Scandinavian journal of clinical and laboratory investigation*, 1980, 40(3):227–32.
14. El-Sonbaty MR, Abdul-Ghaffar NU. Vitamin D deficiency in veiled Kuwaiti women. *European journal of clinical nutrition*, 1996, 50(5):315–8.
15. Stephens WP et al. Observations on the natural history of vitamin D deficiency amongst Asian immigrants. *Quarterly journal of medicine*, 1982, 51(202):171–88.
16. Sedrani SH. Low 25-hydroxyvitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. *Annals of nutrition & metabolism*, 1984, 28(3):181–5.
17. Parfitt AM et al. Vitamin D and bone health in the elderly. *American journal of clinical nutrition*, 1982, 36(5 suppl.):1014–31.
18. Epstein S et al. The influence of age on bone mineral regulating hormones. *Bone*, 1986, 7(6):421–5.
19. Marcus R, Madvig P, Young G. Age-related changes in parathyroid hormone and parathyroid hormone action in normal humans. *Journal of clinical endocrinology and metabolism*, 1984, 58(2):223–30.
20. Chapuy MC, Durr F, Chapuy P. Age-related changes in parathyroid hormone and 25 hydroxycholecalciferol levels. *Journal of gerontology*, 1983, 38(1): 19–22.
21. Bell NH et al. Evidence of a probable role for 25-hydroxyvitamin D in the regulation of human calcium metabolism. *Journal of bone and mineral research*, 1988, 3(5): 489–95.

22. Francis RM, Peacock M, Barkworth SA. Renal impairment and its effects on calcium metabolism in elderly women. *Age and ageing*, 1984, 13(1):14–20.

23. Endres DB et al. Age-related changes in serum immunoreactive parathyroid hormone and its biological action in healthy men and women. *Journal of clinical endocrinology and metabolism*, 1987, 65(4): 724–31.

24. Wiske PS et al. Increases in immunoreactive parathyroid hormone with age. *New England journal of medicine*, 1979, 300(25):1419–21.

25. Sherman SS, Hollis BW, Tobin JD. Vitamin D status and related parameters in a healthy population: the effects of age, sex, and season. *Journal of clinical endocrinology and metabolism*, 1990, 71(2): 405–13.

26. Yendt ER, Cohanim M, Rosenberg GM. Reduced serum calcium and inorganic phosphate levels in normal elderly women. *Gerontology*, 1986, 41(3):325–30.

27. Villareal DT et al. Subclinical vitamin D deficiency in postmenopausal women with low vertebral bone mass. *Journal of clinical endocrinology and metabolism*, 1991, 72(3):628–34.

Meeting in Cairo of the Commission on Social Determinants of Health

The second meeting of the WHO-initiated Commission on Social Determinants of Health took place in Cairo, Egypt from 5 to 7 May 2005. The meeting was inaugurated at the National Council for Women. The Commission is a new body created to spearhead action on the social causes behind ill-health. Launched in Santiago de Chile on 18 March by WHO's Director General Dr LEE Jong-wook and the President of Chile, it is charged with recommending practical action, interventions and policies to improve health and narrow health inequalities through action on social determinants. The Commission will operate until 2008.

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