

Vitamin D status and bone health in immigrant versus Swedish women during pregnancy and the post-partum period

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Abstract

Objective: We evaluated the association between vitamin D status and bone health in pregnant and post-partum immigrant versus Swedish women. **Methods:** We consecutively recruited 41 immigrant and 19 age-matched healthy native Swedish women. Serum 25-hydroxy vitamin D₃ [25(OH)D] and parathyroid hormone (PTH) were analyzed at pregnancy week 12 and 6-12 months postpartum. Dual X-ray absorptiometry (DXA) of the hip and lumbar spine, and peripheral quantitative computed tomography (pQCT) of the radius and tibia were analyzed 6-12 months postpartum. **Results:** The mean±SD 25(OH)D in gestational week 12 was 20±11 nmol/L among the immigrants and 60±17 nmol/L among the Swedish women (p<0.001). The postpartum 25(OH)D was 29±18 nmol/L among the immigrants and 53±19 nmol/L among the Swedish women (p=0.003). BMD measured with DXA and pQCT did not differ significantly between groups. The ratio of cortical and trabecular density, a potential sign of osteomalacia, did not differ between groups. There were no significant correlations between 25(OH)D and the bone density measurements. **Conclusions:** Immigrant young women in Sweden are at a high risk of persistent and pronounced 25(OH)D deficiency. However, radiological measures of bone health were not affected by persisting low 25(OH)D. The health consequences of 25(OH)D deficiency should be studied in future studies.

Keywords: Osteoporosis, Secondary Hyperparathyroidism, Osteomalacia, D-vitamin, DXA

Introduction

Vitamin D is a key regulator of calcium homeostasis and bone turnover. The concentration of 25-hydroxy vitamin D₃ [25(OH)D] in serum is a functional indicator of vitamin D status¹. A persisting low 25(OH)D level will lead to an increase in parathyroid hormone (PTH), which stimulates bone loss². Levels of 25(OH)D<20 nmol/L lead to osteomalacia³. In the Nordic region, sun exposure is insufficient to form enough provitamin-D₃ from September to April. Natives of these countries are partly adapted to these conditions by their light skin and also

by their clothing habits⁴. By contrast, many immigrants living in the northern part of Europe are 25(OH)D deficient^{5,6}.

The optimal serum 25(OH)D level needed to maintain bone health is unknown. Estimates of the optimal level vary from 20 to 110 nmol/L (reviewed by⁷). Whereas hypovitaminosis D in elderly is associated with reduced bone mineral density (BMD)⁸, this association in younger adults is less clear. Several studies have reported absence of association between 25(OH)D levels and BMD^{5,6,9,10}. By contrast, Bishoff-Ferrari et al and Roy et al found significant positive associations between 25(OH)D and BMD^{11,12}. In general, these studies have evaluated BMD on at most two sites.

It is documented that pregnant women have lower vitamin D status; however, we do not know whether this can affect bone health of the women. During pregnancy and lactation mothers require significant amounts of calcium for the fetus and suckling neonate. Maternal adaptations during pregnancy, e.g. increased intestinal absorption, provide the necessary calcium relatively independent of vitamin D¹³. During lactation skeletal calcium is mobilized. However, pregnancy and lactation do not have an overall negative effect upon the maternal

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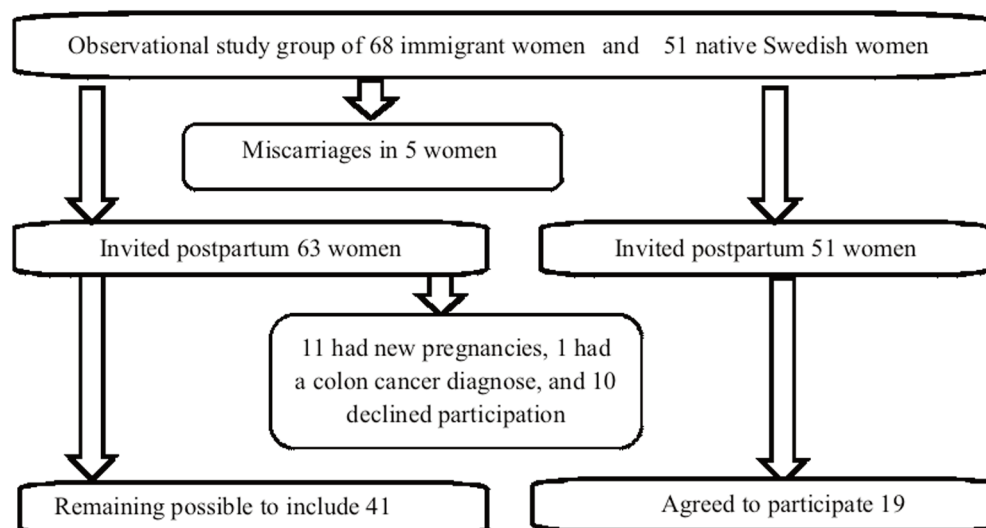


Figure 1.

skeleton¹⁴. It is the child that is at risk of hypocalcemia and bone loss^{13,15}.

One advantage with pQCT is that it can be used to interpret abnormalities of bone material such as osteomalacia, as suggested by Rauch¹⁶. The osteocyte in soft bone with osteomalacia will overestimate the mechanical loads and the trabecular volume BMD will increase, due to increased strain in the cortical undermineralized bone that, on the other hand, goes with a low volume BMD¹⁶. I.e. osteomalacia is associated with a reduced cortical versus trabecular volume BMD.

The uncertainty of the relationship between 25(OH)D deficiency and bone health is particularly important for immigrant women in the Nordic countries, given their high frequency of 25(OH)D deficiency. This question is assessed in this study where we have evaluated vitamin D status and bone health in pregnant and post-partum immigrant versus Swedish women. We performed a comprehensive analysis to evaluate the hypothesis that 25(OH)D status influences BMD evaluated with central dual X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) 6-12 months post partum.

Materials and methods

Subjects

Immigrant women living in Stockholm, Sweden, and non-immigrant pregnant women in gestational week 12 were consecutively recruited between 2006-2009 from antenatal units collaborating with the Karolinska University Hospital Huddinge, Stockholm (58d°N). The immigrant women were originating from Africa, the Middle East, India, Pakistan, Bangladesh and South America. Exclusion criteria were inability to communicate in Swedish, malabsorption, liver and kidney disease, medication for epilepsy, any calcium and/or vitamin D supplementation, severe psychiatric illness and psy-

chological inability to participate in the study. Recruitment of immigrant and Swedish women is described in Figure 1. The inclusion in the study was consecutively in both groups from February to November. The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki. All women received oral and written information and an informed consent was signed prior to their inclusion into the study.

Blood sampling

Blood samples were drawn consecutively from women during pregnancy week 12 and 6-12 months postpartum. We performed repeated measurements to allow evaluation of long term 25(OH)D status. The patients were not fasting. 25(OH)D levels serves as an accurate indication of vitamin D stores obtained from both ultraviolet irradiation and dietary intake over long periods due to the rather long serum half-life¹⁷. 25(OH)D in serum was assayed using a competitive chemiluminiscense assay (CLIA), LIAISON (DiaSorin Inc, Saluggia, Italy) with a total CV less than 8% for samples with a concentration between 25-310 nmol/L (10-128 ng/mL). Intact PTH in plasma was assayed using a Modular Analytic E System (Roche Diagnostics GMBA, Mannheim, Germany) with a total CV less than 3%. Total intact PTH is not affected by feeding¹⁸.

Bone parameters

DXA

The areal bone mineral density of the left femoral neck, the left total hip and the lumbar spine, was measured in each subject at 6-12 months post partum using DXA (GE Lunar iDXA with software en Core 2008 version 12, 30, 008, GE Medical systems, Chalfont St. Giles, UK). Throughout the study automatic calibration checks were performed daily. Three times a

	Immigrants (n=41) ^c	Ethnic Swedes (n=19)	P
Age (years)	31.5 (4.3)	31.9 (4.6)	0.71 ^a
Body height (m)	1.60 (0.06)	1.69 (0.07)	<0.001 ^a
Body weight (kg)	70.5 (13.6)	71.9 (13.9)	0.70 ^a
BMI (kg/m ²)	27.4 (4.6)	25.3 (4.9)	0.10 ^a
25(OH)D (pregnancy week 12) (nmol/L)	20 (11) (10-52)	60 (17) (29-91)	<0.001 ^b
25(OH)D (nmol/L) (postpartum)	29 (18) (10-73)	53 (19) (33-87)	0.003 ^b
PTH (pregnancy week 12) (ng/L)	31 (18) (8-95)	18 (5) (9-29)	0.002 ^b
PTH (ng/L) (postpartum)	69 (35) (28-175)	38 (11) (21-59)	<0.001 ^b

^aT- test.
^bMann-Whitney U-test.
^cThe proportion of white women was 56% and non-white women was 44% in the immigrant group.

Table 1. Baseline characteristics in immigrant and Swedish women presented as mean (SD). Ranges for 25(OH)D and PTH is presented.

week calibration using a spine phantom provided by the manufacturer was performed. The coefficient of variation for the spine phantom testing was 1.5 %. The left hip was scanned in all patients and the lumbar spine was measured by scanning from the first to the fourth lumbar vertebra. The reported precision for this DXA model is about 1%¹⁹.

pQCT

Peripheral quantitative computed tomography (pQCT)²⁰ measurements were carried out using a Stratec XCT-2000 scanner (Stratec, Pforzheim, Germany) and analyzed using Stratec software version 5.5d or 5.40. Images were acquired with an in-plane voxel dimension of 0.5 mm. A scan speed of 20 mm/s was used. For each participant, the non-dominant arm and leg was selected for measurement. Scans were made at sites that contain predominantly trabecular bone (4% sites) and cortical bone (66% and 38% sites in the radius and tibia, respectively). Radial and tibial length was measured to the nearest 0.5 cm using a tape measure. Radial length was defined as the distance from the midpoint of the ulnar styloid process to the olecranon. Tibial length was defined as the distance from the midpoint of the medial malleolus to the medial aspect of the tibial plateau. The following parameters were determined at the selected bone sites: total volumetric bone mineral density (vBMD), trabecular vBMD, cortical vBMD, trabecular content, total cross-sectional area, cortical cross-sectional area, cortical thickness, endocortical circumference, and periosteal circumference. Quality assurance for pQCT was performed on all working days. Reported reproducibility for Caucasian adults at the distal radius is 1.4% for total area, 0.9% for bone mineral content, 1.5% for total vBMD and 0.8% for trabecular vBMD.

Statistical analysis

Statistical comparisons were made with the t-test, linear regression or the Mann-Whitney U-test. Descriptive data was presented as means and standard deviation (SD) and for some variables, ranges. Test of normality was done with visual inspection. Skewness was observed for 25(OH)D and PTH-val-

ues and therefore non-parametric tests were mainly used for these variables. Logarithmic transformation (Ln) of 25(OH)D and PTH revealed a more normal distribution, and in the case of linear regression, Ln25(OH)D and LnPTH was used. The ratio of pQCT-measured cortical density and trabecular density in the radius and the tibia were calculated for comparisons between the two groups. Presented *p*-values are two-sided. Statistical analysis was carried out with IBM SPSS 20.0.

Results

To explore the relationship between 25OHD status and bone health in young adults immigrant women were invited to participate in the present study, which included an evaluation 6-12 months after giving birth. 41 (65% attrition rate) immigrant women were included postpartum, see Figure 1. Those who did not have dark skin covered their arms and legs for clothing habits. 19 (37%) women born in Sweden, who were recruited during the same period and from the same antenatal units, accepted to participate in the study. We did not record endogenous production of vitamin D, i.e., sun exposure. All the subjects were without vitamin D supplementation throughout the study.

Baseline characteristics are shown in Table 1 and are summarized here. The age, body weight and BMI of immigrant and Swedish women were similar. The Swedish women were taller than the immigrants. 44% of the immigrant women had dark skin color. Immigrants had lower mean 25(OH)D level and a higher mean PTH level than Swedish women in pregnancy week 12. The differences in 25(OH)D and PTH levels persisted at least one year, until the follow up examination 6-12 months post partum. 46% of the immigrant women were breastfeeding when DXA was performed and 41% were not. In 12% of the immigrant women information concerning breastfeeding was missing. 47% of Swedish women were breastfeeding when DXA was performed.

Bone density measured with DXA at the femoral neck, total hip and lumbar spine did not differ between immigrants and

DXA	Immigrant women	Ethnic Swedes	<i>P</i>	<i>P</i> Corrected for body height
Femoral neck BMD (mg/cm ²)	0.99 (0.14)	0.98 (0.11)	0.90	0.52
Total hip BMD (mg/cm ²)	1.01 (0.15)	1.00 (0.09)	0.72	0.78
Spine L1-L4 BMD (mg/cm ²)	1.13 (0.15)	1.17 (0.08)	0.32	0.73
pQCT				
Radius total cross-sectional area mm ²	114 (17)	130 (29)	0.017	0.89
Radius trabecular vBMD g/cm ³	181 (46)	178 (48)	0.79	0.93
Radius cortical vBMD g/cm ³	1177 (28)	1171 (26)	0.50	0.72
Radius cortical thickness mm	2.2 (0.3)	2.4 (0.3)	0.14	0.36
Radius endocortical circumference	24 (4)	25 (5)	0.15	0.61
Radius periosteal circumference	38 (3)	40 (4)	0.015	0.95
Radius cortical vBMD/trabecular vBMD	6.9 (1.8)	7.0 (1.8)	0.84	0.85
Tibia total cross-sectional area mm ²	359 (49)	371 (43)	0.45	0.28
Tibia trabecular vBMD mg/cm ³	220 (47)	214 (37)	0.71	0.48
Tibia cortical vBMD g/cm ³	1200 (22)	1197 (20)	0.68	0.88
Tibia cortical thickness mm	4.6 (0.6)	5.0 (0.4)	0.040	0.11
Tibia endocortical circumference	38 (5)	37 (4)	0.41	0.024
Tibia periosteal circumference	67 (5)	68 (4)	0.43	0.29
Tibia cortical vBMD/trabecular vBMD	5.7 (1.1)	5.7 (1.0)	0.87	0.78

^a Due to missing data, DXA results were available in 40 immigrant and 16 Swedish women, pQCT of the radius was available in 29 immigrant and 19 Swedish women, and pQCT of the tibia was available in 26 immigrant and 14 Swedish women. P-values are presented for t-test and, in case of correction, linear regression.

Table 2. Mean value (SD) of the different bone variables in the 41 immigrant and the 19 Swedish women^a.

Swedish women (Table 2). In a secondary analysis, body height was used as a covariate since there was a difference between immigrant and Swedish women.

The pQCT was measured in radius in 29 of the immigrant women. However in three of them their lower leg was too large to perform a pQCT measurement. Therefore, pQCT was available for 26 immigrant women only in the tibia. For the same reason pQCT tibia was available in 14 Swedish women only. For pQCT, mean tibia endocortical circumference was lower in the Swedish women after correction for body height (Table 2). There was no difference between immigrants and Swedish women for pQCT measures of bone mineral density (Table 2).

Both PTH and Alkaline phosphatase (ALP) increase post partum in our patients, however the levels were still in the normal range (unpublished data). The rise in PTH and ALP encouraged us to examine signs of osteomalacia in the cohort according to the suggestion of Rauch¹⁶. Immigrant and Swedish women did not differ in trabecular and cortical volume BMD and the ratio of cortical and trabecular density was compared in the radius, as well as in the tibia, and did not differ between groups (Table 2). Thus, no signs of osteomalacia were found assessed with pQCT.

Finally we evaluated, in joint analysis of immigrant and Swedish women, if 25(OH)D and PTH at 6-12 month post partum was related to the different bone density parameters. There were no significant correlations between 25(OH)D and the different bone density measurements (results not shown). There were no significant correlations between PTH and the different

bone density measurements (results not shown). Linear regression with the different bone density variables as dependent and ln PTH or ln 25(OH)D as independent variables showed results similar to the Spearman correlations. Adding body height as an independent variable did not change this substantially, with corrected p-values ≥ 0.14 for ln25(OH)D and ≥ 0.13 for lnPTH in these analyses (results not shown).

Discussion

The relationship between 25(OH)D levels and bone health in younger adults at a high risk of hypovitaminosis D is unclear. We here report that immigrant young adult women in Sweden are at a high risk of persistent and pronounced 25(OH)D deficiency; their 25(OH)D levels are around half those of native Swedish women. In these women we have performed a comprehensive radiological examination of bone health, including both central DXA and pQCT, and observe no significant differences in bone mineral density between immigrant and native Swedish women, and no correlation between 25(OH)D levels and bone mineral density. Thus, we cannot confirm the hypothesis that 25(OH)D levels regulate BMD in young adults.

Our results, i.e. no association between 25(OH)D levels and measures of bone mineral density are in agreement with finding in a number of other studies examining subjects at a high risk of hypovitaminosis D, in particular immigrants to Nordic countries^{5,6,9,10}, and in contrast to the findings by Bishoff-Fer-

rari et al in the NHANES study¹¹. The cause of this discrepancy is unknown but may include other environmental and health factors that differ between the NHANES and immigrant cohorts. The ethnical difference between the studies may also be of importance.

To our knowledge only one earlier study, from Finland, has used pQCT to evaluate the association between vitamin D status and bone health²¹. In the Finnish study, 25(OH)D levels associated with distal and proximal radius bone mineral density, and the stress-strain index (a measure of bone torsional strength)²¹. We have no obvious explanation for this contrast to our results. However, the Finnish study was larger and did not include women during reproduction.

According to Bahn et al. vitamin D-deficiency in its early stages with increased PTH and elevated ALP may have increased bone turnover but without mineralization defects²². Our study group most certainly had a vitamin D deficiency for at least 12 months. We can assume that they had suffered from vitamin D deficiency longer than this. Therefore, it is unlikely that a short duration of 25(OH)D deficiency can explain the lack of association between 25(OH)D levels and bone mineral density. Furthermore the immigrants and Swedish women did not differ in the ratio of cortical and trabecular density in the radius, as well as in the tibia. This indicates that our patients did not suffer from osteomalacia.

One limitation of our study is that the ethnic heterogeneity both among the immigrant women, and between these women and the Swedish women were not considered. Ethnic differences in bone mineral density have been reported²³. Blacks and Hispanics have higher bone mineral density than whites. The inclusion of immigrants from Africa and South America in our study could therefore potentially mask the negative effect of hypovitaminosis D on bone health of relevance in other ethnic groups. Furthermore, we did not have information on dietary calcium intake or physical activity, and these variables were therefore not adjusted for in our analyses. We think it is inappropriate to adjust for variables that might be related to the immigrant status as such, i.e. immigrants might have another diet.

The DXA was performed 6-12 month post partum. In both groups about 50 % were breastfeeding at the time for DXA performance. Therefore, we do not think that lactation was a confounder in this study. In addition, there are conflicting results as to whether lactation affects BMD²⁴. We do not think seasonal effects on 25(OH)D influenced the results since, first, both groups were ascertained in parallel and, second, the difference in 25(OH)D between groups persisted for at least a year.

Finally, our study encompassed a limited number of women and therefore may therefore not have enough power to detect small effects on bone mineral density. In particular pQCT measurements were missing for some subjects. The low number of Swedish women was due partly to the high frequency of pregnant immigrant women at the antenatal units from which patients were recruited. A post hoc power analyses showed that with the current sample size a 10% difference in femoral neck BMD or a 20% difference in radius trabecular vBMD could have been detected at a power of 80% and alpha

of 0.05. Thus our study cannot exclude an association between 25(OH)D-levels and bone parameters.

In conclusion, radiological measures of bone health are not affected by persisting low vitamin D levels in immigrant women living in Stockholm. Despite a presumably long period of vitamin D-deficiency in immigrant women living in the Nordic region, low 25(OH)D-levels was not associated with poor bone health. Immigrant young adult women in Sweden, irrespectively of their skin color, are at a high risk of persistent and pronounced 25(OH)D deficiency, which warrant clinical attention and supplementation with vitamin D in this group since severe vitamin D deficiency in its late stages can cause osteomalacia.

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