Clinical Nutrition ESPEN 38 (2020) 271–276

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Vitamin D deficiency associated with reproductive factors in northern Iranian women: The PERSIAN Guilan Cohort Study (PGCS)

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ARTICLE INFO

Article history:
Received 4 January 2020
Accepted 23 March 2020

Keywords:
Vitamin D deficiency
Reproductive factors
PERSIAN Guilan cohort study

SUMMARY

Background: One of the public health concerns is Vitamin D deficiency. The aim of this study was to determine the prevalence of vitamin D inadequacy and to determine its reproductive factor correlates in northern Iranian women.

Methods: This study, conducted on 5096 females aged 35–70 years. The study was based on data from PERSIAN Guilan Cohort Study (PGCS), a prospective, population-based cohort study in Guilan, Iran. History of reproductive and gynecologic factors, including age at menarche, age at first marriage, number of pregnancies or live births, age at first pregnancy, duration of breastfeeding, number of abortions, age and type of menopause status, use of oral contraceptives or hormone replacement therapy, history of hysterectomy, tubectomy or oophorectomy and history of gestational diabetes and hypertension was collected. Serum 25(OH) vitamin D was measured.

Results: The mean 25(OH)-D concentration was 21.78 ng/mL, and 53.5% of women had vitamin D inadequacy. The multivariate analyses revealed that younger age (36–45 years) [>66 years adjusted odds ratio (aOR) = 2.1, 95% CI 1.7–2.7, 56–65 years aOR = 1.7, 95% CI 1.3–2.1 and 46–55 years aOR = 1.4, 95% CI 1.1–1.7], not consuming oral contraceptives [aOR = 1.1, 95% CI 1.05–1.3] and pre-menopausal status [aOR = 1.4, 95% CI 1.2–1.6] were significantly independently associated with vitamin D inadequacy.

Conclusion: Vitamin D inadequacy is common in northern Iranian women. The reproductive factors that independently correlated with vitamin D statues are oral contraceptive consumption and menopausal statue.

1. Introduction

Vitamin D, a fat-soluble vitamin responsible for phosphate and calcium absorption, has been traditionally considered as important in maintaining bone health and mineral homeostasis [1,2]. However, during the past decade, findings of several study have revealed that vitamin D produces extra-skeletal effects, including beneficial effects on the cardiovascular and immune systems [3]. Vitamin D deficiency has been associated with numerous health conditions including risk of cancer [4–6], diabetes mellitus [7–9], hypertension and cardiovascular disease [10–13], autoimmune conditions [14,15] and overall mortality although a causal link has not been well-known [16,17].

The vitamin D inadequacy prevalence depends upon the definition used and although by an international conference on "Controversies in Vitamin D″ was held in Pisa, Italy, in June 2017 [18] report is commonly defined as a 25-hydroxyvitamin D serum level ≤50 nmol/L (20 ng/mL) [19–21]. an international conference on "Controversies in Vitamin D″ was held in Pisa, Italy, in June 2017 Published studies have used various cutoff points for vitamin D deficiency. However, by different definitions, vitamin D deficiency

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https://doi.org/10.1016/j.clnesp.2020.03.022
2405-4577/

was found to be one of the common medical conditions worldwide and its prevalence may be increasing globally [22,23] whilst levels below 10 ng/mL are most common in regions such as South Asia and the Middle East [24].

Some evidence suggests that vitamin D has been related to women reproduction [25–28]. For example, vitamin D insufficiency has been associated with increased risks of preeclampsia, gestational diabetes, and small for gestational age infants [29]. Also, studies have shown that vitamin D deficiency may alter the anti-Müllerian hormone, one of the best diagnostic markers of ovarian reserve, expression and serum levels [30] and suggested that low level of vitamin D might predispose females toward earlier menopause [31]. Some studies found a positive association between 25OHD3 serum levels, use of oral contraceptive and menopausal hormone therapy [32–35]. A potential explanation may be that increases the levels of 25OHD3-binding proteins by estrogen [36]. However, apart from this, few researches have reported on vitamin D in relation to reproductive and hormone-related factors in females. Therefore, the aim of this study was to determine the prevalence of vitamin D inadequacy and to determine its reproductive factor correlates in northern Iranian women. This study is a part of The PERSIAN Guilan Cohort Study (PGCS), a prospective, population-based cohort study in Guilan, Iran with the following objectives: (a) To determine the prevalence and incidence of non-communicable diseases, (b) To compare the relationships between risk factors and NCDs (c) to establish a biobank for basic scientific research [37].

2. Materials & methods

2.1. Participants

We evaluated, the women of the PGCS ("PERSIAN Guilan Cohort Study") cohort, a prospective, population-based cohort study in Guilan, Iran which has been previously described in details [37,38]. This study cohort comprises 5094 women 35–70 years of age, recruited between October 8, 2014 and January 20, 2017 from Guilan province, northern Iran, as part of the Prospective Epidemiological Research Studies in Iran (PERSIAN). The PERSIAN Cohort Study is a national study aiming to include 180,000 Iranians aged 35–70 years from 18 geographically distinct areas of Iran (37). Different districts of the Guilan province were chosen to include different socioeconomic status levels including urban areas and 39 villages. This area was selected due to its long-term population stability, high population density, a relative similarity in demographic and behavioral characteristics.

2.2. Data collection

2.2.1. Demographic, gynecologic and reproductive variables

Data were collected using a face-to-face interview format by trained interviewers [38]. Age, educational level, habitat and marital state were collected as demographic variables. Comprehensive information was recorded on reproductive and gynecologic history, including age at menarche, age at first marriage, number of pregnancies, age at first pregnancy, number of live births, duration of breastfeeding, number of abortions, age and type of menopause status, oral contraceptives (OCP) or hormone replacement therapy (HRT) consumption, history of hysterectomy, tubectomy or oophorectomy and History of gestational diabetes and gestational hypertension. Also, data of vitamin D supplementations use include ampule or Pearl of vitamin D, multivitamin mineral, and calcium D was collected.

2.2.2. Vitamin D measures

Blood samples were collected from each participant using Vacutainers (Greiner Bio-One International GmbH, Kremsmunster, Austria). EDTA (K3) tubes (Becton Dickinson, France) were used to Whole blood samples collection. The 25 (OH) D Concentrations was measured by using a commercially available electrochemiluminescence immunoassay with Roche Elecsys 2010 and

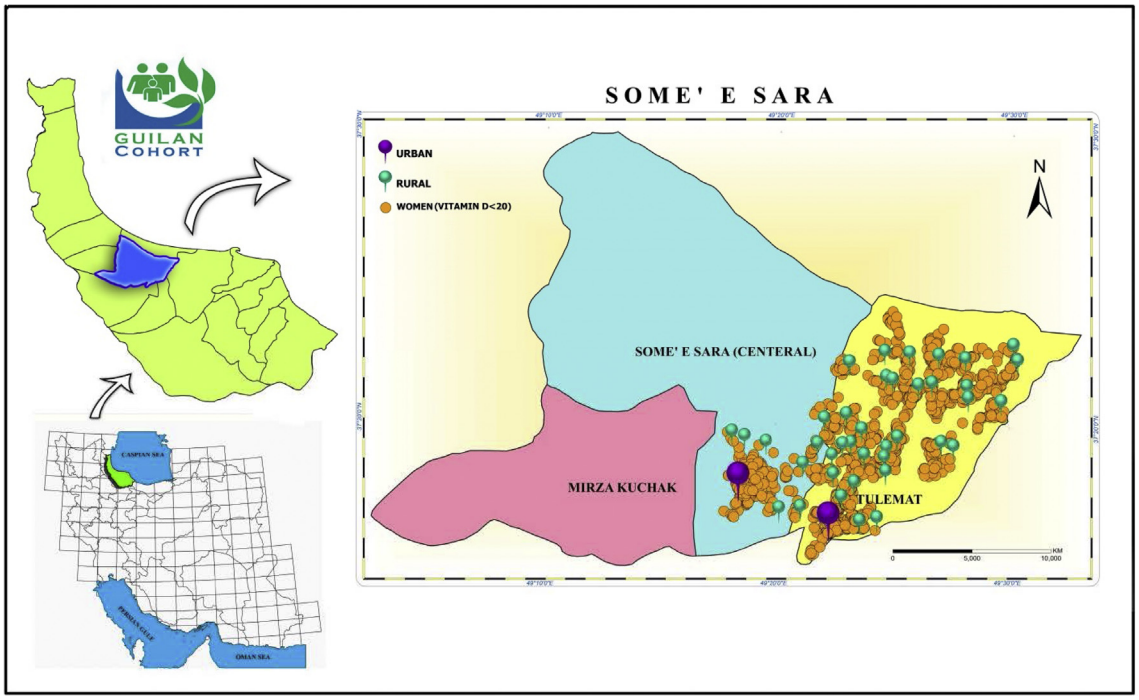

Fig. 1. Geographical location of participants with vitamin D deficiency (25(OH)-D concentration ≤ 20 ng/mL).

Table 1
Demographic profile and reproductive factors of study population according to serum 25-OH D levels.

Vitamin D level	Vitamin D SUFICENT >20 ng/mL (50 nmol/L)	Vitamin D INSUFISION 12–20 ng/mL (30–50 nmol/L)	Vitamin D DEFICENT (<12 ng/mL (30 nmol/L))	P_value*
No. of women (total = 5096)	2367 (46.4%)	1540 (30.2%)	1189 (23.3%)	
Age at selection, a mean yrs (SD)	53.02 (9)	51.1 (8.8)	49.1 (8.4)	<0.001
Residence, no. of Urban (%)	(1096)46.3	(823)53.4	(489)41.1	<0.001
Marital state, no. of married (%)	(1991)84.1	(1326)86.1	(1011)85	0.2
Educational level, no. of high school or less (%)	(1052)44.4	(663)43.1	(474)39.9	0.03
Vitamin D supplement use, no. of ever (%)	(457)19.3	(319)20.7	(181)15.2	0.001
Vitamin D supplements use, no. of at least monthly (%.)[c]	(69)2.9	(54)3.5	18 (1.5)	0.006
Age at first marriage, mean yrs (SD)	20.8 (5.2)	21.1 (5.5)	21.2 (5.3)	0.08
No. of pregnancies, no. (%)				
0	(77)3.3	(62)4	(54)4.5	<0.001
1-2	(640)27	(452)29.4	(410)34.5	
3+	(1650)69.7	(1026)66.6	(725)61	
Number of livebirths, no. (%)				
Nulliparous	(28)1.2	(28)1.8	(16)1.3	<0.001
1-2	(872)36.8	(606)39.4	(554)46.6	
3+	(1467)62	(906)58.8	(619)52.1	
Age at first pregnancy, mean yrs (SD)	21.8 (5)	22 (5.2)	22.2 (5)	0.1
Duration of breastfeeding, no. of 12 month or more (%)	(1948)82.3	(1261)81.9	(976)82.1	0.9
Abortions, no. of ever (%)	(907)38.3	(574)37.3	(441)37.1	0.7
Hysterectomy, no. of (%)[b]	(265)21.9	(117)17.7	(66)15.8	0.008
Tubectomy, no. of (%)	(564)23.9	(386)25.1	(295)24.9	0.6
History of gestational diabetes, no. of (%)	(86)3.7	(68)4.5	(66)5.7	0.1
History of gestational hypertension, no. of (%)	(95)4.1	(53)3.5	(63)5.4	0.1
Age at menarche, mean yrs (SD)	12.6 (1.4)	12.7 (1.6)	12.6 (1.4)	0.06
Oral contraceptive use, no. of ever (%)[a]	(1493)63.3	(915)59.6	(692)58.2	0.005
Post-menopausal, no. (%)	(1209)51.1	(661)42.9	(419)35.2	<0.001
Age at menopause, mean yrs (SD)[b]	47.4 (5.7)	47.5 (6)	47.3 (5.3)	0.9
Type of menopause, no. of natural (%.)[b]	(827)68.5	(471)71.3	(312)74.5	0.06
Hormone replacement therapy, no. of ever (%)[a,b]	(40)3.3	(15)2.3	(11)2.6	0.5
Oophorectomy, no. (%)[b]	(168)13.9	(71)10.7	(48)11.5	0.1

SD = standard deviation (in parentheses).
No. = number.
Note: The number in the analyses may vary due to missing data.
[a] Three months or longer.
[b] Postmenopausal women only.
[*] Statistical significance based on the ANOVA for continuous variables or Chi-square test for categorical variables.

Cobas E411 auto analyser (Roche Diagnostics GmbH, Mannheim, Germany).

The 25 (OH) D Concentrations that was less than 12 ng/mL (30 nmol/L) was defined as vitamin D deficiency, 12–20 ng/mL (50 nmol/L) was defined as vitamin D insufficiency (≤20 defined as vitamin D inadequacy) and greater than 100 ng/mL (250 nmol/mL) was defined as vitamin D toxicity [18].

2.2.3. Ethics approval

Ethical approval for all parts of the cohort was obtained from the local ethical committee and written informed consent was obtained from each participant [39].

2.3. Statistical analyses

Differences in collected variables between the vitamin D status groups (sufficient, deficiency, insufficiency) were analyzed using the chi square test and ANOVA followed by a Bonferroni.

To find the independent relation between vitamin D inadequacy and a set of explanatory variables, univariate and multivariate logistic regression model were used and unadjusted and adjusted odds ratios and 95% CI were calculated.

The data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). A P-value of less than 0.05 was considered as significant.

3. Results

A total of 5096 women aged 35 years to 70 were enrolled in this study. The mean age of the study population was 51.53 ± 8.9 years. About 47% of participants were from urban areas and 57% of the study papulation were educated diploma or more.

The mean ± SD of 25(OH)-D concentration were 21.78 ± 13.1 ng/mL in the study population. Overall, 23.3% of participants had a 25(OH)-D concentration < 12 ng/mL, and were defined as vitamin D deficiency and 30.2% of them had a 25(OH)-D concentration 12–20 ng/mL, and were defined as vitamin D insufficiency. Geographical location using Garmin GPSMAP 78s of participants that had a 25(OH)-D concentration ≤ 20 ng/mL (vitamin D inadequacy) are shown in Fig. 1.

The Demographic profile and the reproductive factors of study participants, according to serum 25-OH D levels are presented in Table 1. Subjects with vitamin D deficiency were significantly more likely to be from rural areas, had a diploma or more education level, not consuming Vitamin D supplements ever or monthly and to be younger age (all P value < 0.05) (Table 1).

In reproductive and sex hormone-related aspects, having three or more live births, having three or more pregnancies, OCP use, History of hysterectomy and post-menopausal women were significantly more common among Participant with sufficient vitamin D level (all P value < 0.05) (Table 1).

In univariate analysis, younger age at selection, higher education level, older than 23 years at first marriage, two or less Number of pregnancies, two or less Number of livebirths, older than 25 years at first pregnancy, older than 25 years at first livebirth, not OCP use, pre menopause were associated with vitamin D

Table 2
Crude and Independent correlates of vitamin D deficiency from logistic regression analysis.

Variables	vitamin D inadequacy (≤20 ng/mL (50 nmol/L))					
	Unadjusted			Adjusted*		
	OR	(95%CI)	p-value	OR	(95%CI)	p-value
Age at selection (year)						
36-45	2.9	2.5–3.1	<0.001	2.1	1.7–2.7	<0.001
46-55	1.8	1.5–2.3	<0.001	1.7	1.3–2.1	<0.001
56-65	1.3	1.1–1.7	<0.001	1.4	1.1–1.7	0.002
≥66 (ref)	–	–	–	–	–	–
Educational level						
high school or less (ref)	–	–	–	–	–	–
diploma or more	1.1	1–1.2	0.04	0.9	0.8–1.1	0.4
Vitamin D supplement use						
never (ref)	–	–	–	–	–	–
Ever[b]	0.9	0.8–1.07	0.3			
Vitamin D supplement use (at least monthly)[b]						
No(ref)	–	–	–	–	–	–
yes	0.9	0.6–1.2	0.5			
Residence						
Urban (ref)	–	–	–	–	–	–
Rural	0.9	0.8–1.1	0.2			
Age at first marriage						
<23 (ref)	–	–	–	–	–	–
≥23	1.1	1.02–1.3	0.02	1	0.8–1.2	0.7
Number of pregnancies						
0-2	–	–	–	–	–	–
3+(ref)	1.4	1.2–1.6	0.001	1	0.8–1.1	0.9
Age (yrs) at first pregnancy						
<21 (ref)	–	–	–	–	–	–
21-24	1.1	0.8–1.1	0.9	0.7	0.4–1.3	0.3
25+	1	1.02–1.3	0.01	0.5	0.2–1.3	0.2
Number of livebirths						
0-2	–	–	–	–	–	–
3+(ref)	1.4	1.2–1.6	0.001	1	0.8–1.2	0.6
Age (yrs) at first livebirth						
<21 (ref)	–	–	–	–	–	–
21-24	1.1	0.8–1.1	0.9	1.2	0.7–2.1	0.4
25+	1	1.03–1.3	0.01	1.8	0.8–4.1	0.1
OC use						
Ever b (ref)	–	–	–	–	–	–
Never	1.2	1.1–1.3	0.001	1.1	1.05–1.3	0.005
Menopausal status						
yes (ref)	–	–	–	–	–	–
No	1.5	1.4–1.7	0.001	1.4	1.2–1.6	0.001
Type of menopause [b]						
Artificial (ref)	–	–	–	–	–	–
Natural	1.2	1.01–1.4	0.03	1	0.7–1.2	0.9
Hysterectomy [b]						
No	–	–	–	–	–	–
Yes(ref)	1.4	1.2–2	0.003	1.1	0.5–1.2	0.1
Oophorectomy [b]						
No	–	–	–	–	–	–
Yes(ref)	1.4	1.1–2	0.03	1.1	0.6–1.3	0.8

CI = 95% confidence interval.
*Adjusted for all variables that were significant in univariate analyses.
[a] Three months or longer.
[b] Postmenopausal women only.

inadequacy (≤20 ng/mL) and not hysterectomy, not Oophorectomy or natural menopause were associated with vitamin D inadequacy in post-menopausal women (all P value < 0.05) (Table 2). All variables with a significant bivariate association with vitamin D insufficiency (P value < 0.05) were examined in a multivariate logistic regression model. The multivariate analyses revealed that younger age, not consuming OCP and pre-menopausal women were significantly independently associated with vitamin D inadequacy (all P value < 0.05) (Table 2).

The relationships between vitamin D inadequacy and menopausal status by age group are demonstrated in Fig. 2. In 36–45 and 46–55 age group there was a significant independent association between vitamin D inadequacy and menopausal status (adjusted Odds ratio = 2.2, aOR = 1.3 respectively, P value < 0.05) (Fig. 2).

4. Discussion

The current study examined 25(OH)-D levels, the prevalence of vitamin D inadequacy and its association with reproductive factors in north Iranian women. Overall, we demonstrate that vitamin D inadequacy was prevalent in this population, and that the prevalence was particularly high in premenopausal women, those with a younger age, and those who not consume OCP.

Using the definition of serum 25(OH)-D concentrations ≤20 ng/mL, we found that over 53% of north Iranian women would be considered as vitamin D deficient and insufficiency (23.3%, 30.2% respectively). Although different cutoff points have been used to define vitamin D inadequacy, several researches have reported a high prevalence rate of vitamin D inadequacy in Iranian women [40]. The high prevalence of vitamin D inadequacy in the Iranian population may be due to several factors such as the skin pigmentation, intakes of vitamin D, and genetic factors such as vitamin D receptor polymorphisms [41].

In the current study, a young age was a risk factor for vitamin D inadequacy independently. This finding was consistent with some studies [42,43]. The magnitude of sun exposure is a probable factor that contributes to this phenomenon. Because of cosmetic issues, young people may use more sunscreen, and therefore have less exposure to the sun (43). However, others have demonstrated vitamin D deficiency to be more common among elderly people [44], which could be caused by decreased ability to production in the skin poor in the skin [45]. A main reason for the difference between our and these studies may be related to study population that the females up until the age of 70 years included in the current study, and deficiency associated with higher age may not be apparent until later.

We found a correlation between serum levels of 25OHD and menopausal status. Our finding revealed that the risk of vitamin D inadequacy was almost less among postmenopausal women compared with pre-menopauses and this association was more prominent in 36–45 age groups. It means early menopause, less than 45 years old is a protective factor for vitamin D inadequacy independently. other studies found no correlation between menopausal status and vitamin D deficiency [46], although postmenopausal women had slightly higher level of 25OHD [47]. The reason of this difference may be due to not age subgroup analyses in mentioned researches separately. The correlation between vitamin D deficiency and menopausal status is still unknown.

The association between OCP use for three months or longer and sufficient serum levels of 25OHD was found in the current study. This is in line with several previous studies [47,48].A potential explanation may be due to increases in the levels of 25OHD3-binding proteins by estrogen [36]. The relation between type of OCP and serum levels of 25OHD was not evaluate in the current study.

Although, in current study univariate analyses have demonstrated vitamin D inadequacy were associated with 2 or less number of pregnancies or livebirths, older than 25 years at first pregnancy, not hysterectomy and oophorectomy, but we found no independent association between mentioned reproductive factors and vitamin D inadequacy after adjusting for other factors include age and menopausal status by multivariate analyses. This finding is consistent with other study [46].

The strengths of this study are the large sample size and also the population-based data. However, there was a limitations recognized in the current study. Determination of the cause-effect nature of the association between vitamin D level and its correlates not permit with Cross-sectional data.

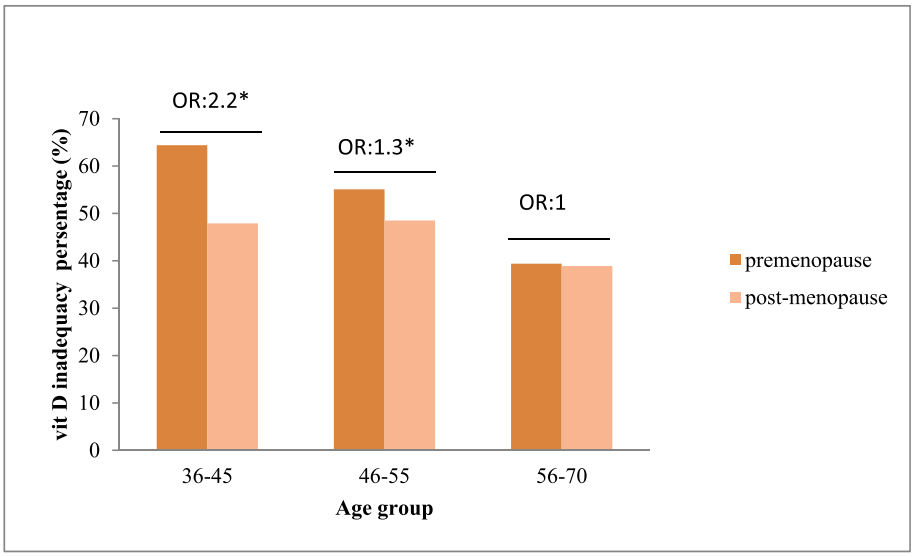

Fig. 2. The prevalence of vitamin D inadequacy by age and menopausal status (OR = adjusted Odds ratio by multivariate analysis (*P = 0.001).

5. Conclusion

In conclusion, our data revealed that vitamin D inadequacy is common in northern Iranian women. The reproductive factors that independently correlated with vitamin D inadequacy are oral contraceptive consumption and menopausal status, such a way that the vitamin D inadequacy was particularly high in women, those who were younger and pre-menopause and who did not custom OCP.

Ethical approval

Ethical approval for all parts of the cohort was obtained from the local ethical committee of Guilan University of Medical Sciences, Rasht, Iran (Ethic code: IR.GUMS.REC.1397.129).

Authorship contribution

Study conception and design: F.J, M.N and F.M.
Acquisition of data: S.H and S.FA.
Statistical analysis: F.J, M.N and S.H.
Interpretation of results: F.J, F.M, S.FA and A.P.
Drafting of manuscript: F.J, M.N, and S.H.
All authors approved the final version of the article, including the authorship list.

Consent for publication

All authors agreed to the submission and approved the final version of the manuscript.

Declaration of Competing Interest

All authors declare that they do not have any study-related conflicts of interest.

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