Original Article

Seasonal vitamin D and bone metabolism in women of reproductive age in urban Beijing

Liying Yang MSc, Wei Zhang PhD

Department of Neonatal Intensive Care Unit, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China

Background and Objectives: This study aimed to evaluate the relationship between serum 25-hydroxy-vitamin D and bone metabolism in healthy women of reproductive age. **Methods and Study Design:** This study included 100 healthy female residents of Beijing (23-30 years old), who underwent bone ultrasonography as well as testing to evaluate serum25-hydroxy-vitamin D, parathyroid hormone, bone alkaline phosphatase, calcium, sodium, phosphorus, and alkaline phosphatase. **Results:** Mean 25-hydroxy-vitamin D in the winter (22.3±3.55 nmol/L) was significantly lower than that in the summer (46.2±16.3 nmol/L). In the winter, a negative correlation was observed between 25-hydroxy-vitamin D and parathyroid hormone(r=0.300, p=0.002) and bone alkaline phosphatase (r=0.274, p=0.016). In the summer, a negative correlation was observed between 25-hydroxy-vitamin D and parathyroid hormone (r=0.386, p<0.001) and bone alkaline phosphatase (r=0.523, p<0.001). Serum calcium, sodium, phosphorus, and alkaline phosphatase were within the normal ranges for both winter and summer, and exhibited no significant correlations with serum 25-hydroxy-vitamin D. The mean speed of sound during bone ultrasonography was 4,125±365 m/s, and a linear correlation was observed between 25-hydroxy-vitamin D and the speed of sound(r=0.215, p=0.031). Serum alkaline phosphatise was not correlated with bone alkaline phosphatase. **Conclusion:** Serum vitamin D deficiency was common among healthy women of childbearing age in Beijing during both winter and summer. Furthermore, bone ultrasonography findings and serum vitamin D, parathyroid hormone, and bone alkaline phosphatase accurately reflected these women's bone metabolism status.

Key Words: reproductive age, vitamin D, bone ultrasonography, parathyroid hormone, bone alkaline phosphatase

INTRODUCTION

Vitamin D is a fat-soluble vitamin that regulates calcium and phosphorus metabolism, which controls the growth, development, and maintenance of the normal skeletal and muscular systems. Unfortunately, low vitamin D concentration is associated with the incidence of cancer, autoimmune diseases, infectious diseases, and cardiovascular diseases.[1] Furthermore, vitamin D deficiency is widespread among the Chinese population, and the average serum 25-hydroxy-vitamin D (25OHD) concentration among the Shanghai population is 44.9±15.9 nmol/L. Moreover, the incidence of vitamin D deficiency and insufficiency tends to increase with increasing age.[2]

In humans, serum 25OHD is the main reserve of vitamin D, and measuring 25OHD is the gold-standard method for evaluating vitamin D status, given 25OHD's good stability, long half-life (2 weeks), and high concentration in the blood.[3] Furthermore, 25OHD accurately reflects the vitamin D concentration that is derived from dietary absorption and skin synthesis.[4] However, there is no ideal cutoff value for serum 25OHD to evaluate vitamin D status, although serum 25OHD concentrations of >75 nmol/L have been reported to indicate the ideal vitamin D status for healthy bone growth.[5] Nevertheless, vitamin D deficiency and insufficiency are increasingly serious global problems, and the latest data from the National Health and Nutrition Examination Survey revealed that >90% of non-Caucasian Americans and >75% of Caucasian Americans have vitamin D deficiency (25OHD of <75 nmol/L).[1] Approximately 70.4% of Latin American women have vitamin D deficiency.[6] Moreover, vitamin D deficiency and insufficiency are prevalent among Chinese individuals of almost all ages and regions,[7] and the average serum 25OHD concentration is 34.0 nmol/L among Japanese women who are <30 years old.[8] Vitamin D deficiency is even more common among Arabic women, and its prevalence is as high as 99.2% in Syria.[9]

There are few studies regarding vitamin D concentration and its relationship with bone metabolism among healthy women who are of childbearing age. Unfortunately, vitamin D insufficiency or deficiency is harmful to pregnant women and has long-term adverse effects on their infants. Seasonal variations in exposure to sunlight (high exposure during the summer, low exposure during the winter) are thought to affect serum vitamin D concen-

Corresponding Author: Dr Wei Zhang, Department of Neonatal Intensive Care Unit, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, No 251, Yaojiayuan Street, Chaoyang district, Beijing, China.
Tel: +86-10-52273708
Email: zw29996@163.com
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trations. Therefore, to examine the relationship between vitamin D status and bone metabolism among healthy women of childbearing age, the present study was designed to examine serum 25OHD concentration and bone metabolism parameters and the seasonal changes in these parameters in this group of women.

MATERIALS ANDMETHODS

Subjects

We recruited healthy women who were of childbearing age (23-30 years old) from the Beijing Obstetrics and Gynecology Hospital. All recruited women worked indoors, and we excluded women with hypertension, diabetes, anemia, heart disease, chronic kidney disease, or other chronic diseases. In total, 100 women met the inclusion criteria and were included in the analysis. This study was approved by the Beijing Obstetrics and Gynecology Hospital Ethics Review Committee, and all participants provided written informed consent.

Data collection

All participants completed a questionnaire regarding their socio demographic characteristics, lifestyle, and dietary intake. The dietary parameters of this questionnaire evaluated the participants' intake of milk, eggs, fish, seafood, organ meats, vegetables, fruit, and vitamin D supplements. The participants were classified according to their education level, with a low education level being defined as completing junior school (31 cases, 31%), a moderate education level was defined as completing high school or technical secondary schooling (30 cases, 30%), and a high education level was defined as completing college or further education (39 cases, 39%).

Measuring height and weight

Height was measured using a metal vertical height measuring gauge, which was placed on a steady level surface and calibrated before the measurements. Trained researchers measured and recorded each participant's height in meters to two decimal places. Digital electronic scales were calibrated and used to measure body mass in kilograms to two decimal places. Body mass index (BMI) was calculated as kg/m^2, and the normal range for Chinese women was defined as 18-25 kg/m^2.

Measurement of sunlight exposure

The subjects self-reported their average daily sunlight exposure time during the winter and summer, and these answers were evaluated by asking questions regarding their exposure during leisure time.

Measuring bone metabolism indicators

Serum concentrations of 25OHD, parathyroid hormone (PTH), calcium, sodium, phosphorus, alkaline phosphatase, and bone alkaline phosphatase were measured in the summer and in the winter. All patients provided a 5-mL fasting blood sample in the morning after an overnight fast, and the serum was separated within 1 h and stored at –80°C for testing on the same day. All calcium, sodium, phosphorus, and alkaline phosphatase measurements were performed using the DXC8000 whole blood biochemistry analyser (Beckman Coulter, Brea, CA). All 25OHD and bone alkaline phosphatase measurements were performed using an ELISA kit from IDS Co. (UK), and PTH levels were measured using an ELISA kit from Biomerica Inc. (Monrovia Aenue Newport Beach, CA).

Bone ultrasonography

Bone ultrasonography was performed in the summer using the Omnisense 7000PQuantitative Ultrasound Instrument (Sunlight, Israel) to measure the speed of sound (SOS; m/s) on the day of blood sampling. The SOS measurement was performed at the midpoint of the left radius for all participants, and the result was compared with the value from the right radius. The probe was calibrated before the measurements, and all measurements were performed by a single operator.

Measurement of 25OHD for defining vitamin D status

Based on participants' serum 25OHD concentrations, vitamin D status was defined as deficiency (≤25 nmol/L), insufficiency (25-50 nmol/L), adequate (50-75 nmol/L), or sufficient (>75 nmol/L).[10]

Statistical analysis

All statistical analyses were performed using SPSS software (version 18.0; SPSS Inc., Chicago, IL). The paired t-test was used to compare the summer and winter values. Categorical variables between groups and the values in winter and summer were compared using the chi-square test or Fisher exact test. Linear regression analysis was performed to analyze the relationships between serum 25OHD concentration, bone ultrasonography findings, and serum concentrations of calcium, sodium, phosphorus, alkaline phosphatase, PTH, and bone alkaline phosphatase. Data are presented as mean±standard deviation, and differences with a p-value of <0.05 were considered statistically significant.

RESULTS

The average age of the 100 participants was 25.8±2.74 years, and the average height was 1.63±0.04 m. There were significant differences in physical activity and sunlight exposure between summer and winter, although there were no differences in supplement use (Table 1). Furthermore, there were no differences in nutrient intake between summer and winter (Table 2). The serum concentrations of 25OHD, PTH, and bone alkaline phosphatase in the winter were significantly different from those in the summer, although there were no significant differences for BMI or concentrations of calcium, sodium, phosphorus, and alkaline phosphatase (Table 3).

In the winter, the mean 25OHD concentration was 22.3±3.55 nmol/L, 89% of the women exhibited vitamin D insufficiency, and 11% of the women exhibited vitamin D deficiency. None of the women had an adequate or sufficient serum vitamin D concentrations. The mean serum PTH concentration was 97.2±25.2 pg/mL, and 10% of the women exhibited high PTH concentrations (normal range: 8.8-68.0 pg/mL). The mean bone alkaline phosphatase concentrations were 43.0±18.1 μg/L (normal: 8.7±5.8 μg/L). In the winter, we observed a negative correlation between serum concentrations of 25OHD and PTH ($r=0.300$, $p=0.002$) and bone alkaline phosphatase

Table1. Subject characteristics

Parameter	Winter (n=100)	Summer (n=100)	X^2	*p*-value
Use of vitamin D			0.156	0.925
Every day	20	22		
Occasionally	46	46		
None	34	32		
Sunlight exposure (h/week)			15.4	<0.0001
<1	54	32		
1-2	20	45		
>2	26	23		
Frequency of physical activity (h/week)			8.52	0.014
<3	60	40		
3-6	19	33		
>6	21	27		

Table 2. Comparison of dietary parameters between winter and summer

Parameter	Winter (n=100)	Summer (n=100)	X^2	*p*-value
Eggs			0.112	0.946
Never	5	5		
1-6 times/week	25	23		
Every day	70	72		
Deep sea fish			0.083	0.960
Never	6	7		
1-6 times/week	88	87		
Every day	6	6		
Milk			0.131	0.937
Never	6	5		
1-6 times/week	82	82		
Every day	12	13		
Other fish			0.144	0.931
Never	7	8		
1-6 times/week	86	86		
Every day	7	6		
Meat			0.277	0.871
Never	7	8		
1-6 times/week	81	78		
Every day	12	14		
Vegetables				1.000†
Never	0	0		
1-6 times/week	3	2		
Every day	97	98		
Animal liver			0.255†	0.907†
Never	9	10		
1-6 times/week	87	85		
Every day	4	5		
Other organ			0.968	0.616
Never	9	13		
1-6 times/week	86	81		
Every day	5	6		
Other milk product			0.125	0.940
Never	7	6		
1-6 times/week	83	83		
Every day	10	11		
Salt			0.428†	0.897†
<3 g/day	9	7		
3-6 g/day	87	88		
>6 g/day	4	5		
Fruit			0.543	0.762
Never	6	4		
1-6 times/week	81	81		
Every day	13	15		

†Fisher exact test: more than 20% of the lattice theory of frequency T <5 or any theoretical frequency T <1.

Table 3. Comparison of laboratory parameters between winter and summer

Parameter	Winter (n=100)	Summer (n=100)	t-value	*p*-value
Serum calcium (mmol/L)	2.24±0.08	2.21±0.11	1.95	0.054
Serum phosphorus (mmol/L)	1.24±0.15	1.29±0.24	–1.56	0.122
ALP (IU/L)	48.8±10.0	46.4±11.0	1.42	0.158
PTH (pg/mL)	97.2±25.2	44.6±23.0	15.4	<0.0001
25OHD (nmol/L)	22.2±3.55	46.2±16.3	–15.1	<0.0001
BAP (μg/L)	43.0±18.1	18.7±10.9	11.529	0.000
Serum sodium (mmol/L)	138±3.42	138±3.46	0.916	0.362
BMI (kg/m^2)	20.3±1.95	20.3±2.02	–0.204	0.839

ALP: alkaline phosphatase; PTH: parathyroid hormone; 25OHD: 25-hydroxy-vitamin D; BAP: alkaline phosphatase; BMI: body mass index.
Data are presented as mean±standard deviation.

(r=0.274, *p*=0.016) (Figure 1). No correlations were observed for serum 25OHD concentration and serum concentrations of calcium, sodium, phosphorus, or alkaline phosphatase (r=0.092, *p*=0.362; r=0.021, *p*=0.836; r=0.052, *p*=0.606; and r=0.135, *p*=0.181, respectively).

In the summer, the mean 25OHD concentration was 46.2±16.3 nmol/L, 62% of women exhibited vitamin D insufficiency, 4% of women exhibited vitamin D deficiency, 30% of women exhibited adequate levels of serum vitamin D, and 4% of women exhibited vitamin D sufficiency. The mean serum PTH concentration was 44.6±23.0 pg/mL, and 13% of women exhibited high PTH. The mean bone alkaline phosphatase concentration was 18.7±10.9 μg/L. A negative correlation was observed between the serum 25OHD concentration and PTH concentration (r=0.386, *p*<0.001) and bone alkaline phosphatase (r=0.523, *p*<0.001) (Figure 1). No correlations were observed for serum 25OHD concentration and serum concentrations calcium, sodium, phosphorus, or alkaline phosphatase (r=0.058, *p*=0.567; r=0.065, *p*=0.522; r=0.077, *p*=0.447; and r=0.142, *p*=0.148, respectively).

Bone ultrasonography findings in the summer

In the summer, the mean SOS value was 4,125±365 m/s, and the SOS values exhibited a negative linear correlation with serum 25OHD concentrations(r=0.215, *p*=0.031) (Figure 1).

Serum alkaline phosphatase and bone alkaline phosphatase

Serum concentrations of alkaline phosphatase were not correlated with bone alkaline phosphatase for winter and summer (r=0.135, *p*=0.181; r=0.130, *p*=0.198; respectively).

DISCUSSION

Analysis of the reasons for low vitamin D concentration during the summer in women of childbearing age

Serum vitamin D concentration is affected by age, sex, and genetic, cultural, seasonal, geographical, and other factors. Furthermore, vitamin D can be found in fish, animal liver, eggs, lean meat, skim milk, cheese, cod liver oil, nuts, seafood, and vitamin D-fortified foods. Vitamin D is mainly found in animal-derived foods, and plant-derived foods contain almost no vitamin D. Moreover, vitamin D can be synthesized in the skin, although this requires exposure of the skin to the sun and its ultraviolet irradiation. When sunlight is present, 7-dehydrocholesterol in the skin can be converted into vitamin D3, and vitamin D3 is then converted into 1,25$(OH)_2D3$, with the liver and kidney playing roles in this conversion. However, the main source of vitamin D is via skin exposure to sunlight, and regular exposure to the sun is critical to prevent vitamin D deficiency.

The present study revealed that the daily dietary intakes among women of childbearing age were not significantly different between winter and summer, especially regarding their intake of foods and supplements that are rich in vitamin D. In the summer, these women had relatively high outdoor sun exposure and exercise levels, which contributed to the higher vitamin D levels (vs those in winter), although the serum vitamin D levels were not ideal in either season.

In this context, there are many factors that can affect vitamin D concentration in women of childbearing age. First, Beijing is an inland city and the population consumes relatively small amounts of deep sea products (vs coastal cities), which are rich in vitamin D. Second, the Chinese diet mainly consists of grain- and vegetable-based foods, which contain very low amounts of vitamin D. Third, the subjects in the present study were indoor workers, who would have limited exposure to the sun during the winter, as Beijing's geographical location receives a limited number of hours of sunlight during the winter. In contrast, the women might receive greater sunlight exposure during the summer, as their outdoor activities and sports participation increased during this period. Nevertheless, the temperature during the summer is high, which might limit outdoor activity and sunlight exposure. Fourth, air pollution in Beijing has recently reached serious levels, with extremely high levels of particulate matter with a diameter of 2.5 μm, which may also affect outdoor activity and sunlight exposure. Fifth, greater concern regarding skin cancer may motivate individuals to use protection (e.g., clothing coverage or sunscreen), which may limit their sunlight exposure, even during the summer.

The relationships between vitamin D and PTH, bone alkaline phosphatase, and bone ultrasonography findings

The parathyroid gland is highly stimulated during vitamin D deficiency, which can result in secondary hyperparathyroidism. Furthermore, several studies have reported a

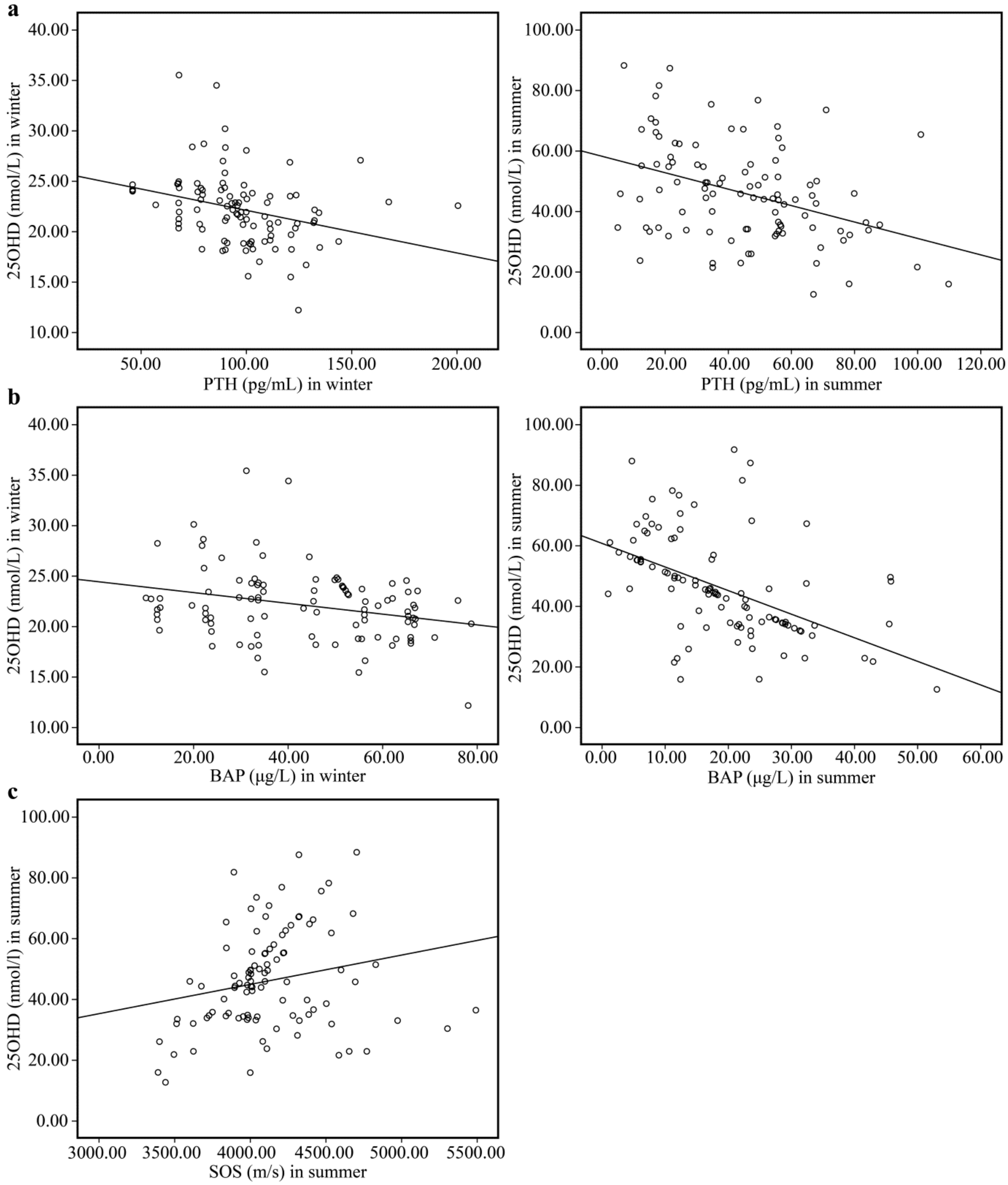

Figure 1. The relationship between serum 25-hydroxy-vitamin D (25OHD) and parathyroid hormone (PTH), bone alkaline phosphatase (BAP), and bone ultrasonography findings (speed of sound [SOS] at the radius). a) A negative linear correlation is observed between 25OHDand PTH in the winter (r=0.300, p=0.002) and in the summer (r=0.386, p<0.001). b) A negative linear correlation is observed between 25OHDand BAP in the winter (r=0.274, p=0.016) and in the summer (r=0.523, p<0.001). c) A positive linear correlation is observed between 25OHDand SOS findings in the summer (r=0.215, p=0.031).

significant negative correlation between serum concentrations of 25OHD and PTH,[11] which we confirmed in the present study.

Alkaline phosphatase can act as a hepatic, bony, intestinal, renal, or placental isozyme, depending on the site of its production. The serum alkaline phosphatase concentration represents the total activity of enzymes produced by various issues. However, because of its low specificity and sensitivity as well as the significant effects of tissue-specific diseases, serum alkaline phosphatase concentration only provides a general estimate of bone metabolism status. In contrast, bone alkaline phosphatase is produced by osteoblasts and accurately reflects bone metabolism status, because it is not influenced by disorders in other tissues. When bone formation is more rapid than bone resorption, serum bone alkaline phosphatase activity increases significantly and acts as a sensitive indicator for osteoblast activity and bone formation. However, low blood calcium concentration results in increased PTH concentration, which stimulates the production of 25OHD by the kidney. This activates feedback between osteoblasts and osteocytes, which results in the release of bone alkaline phosphatase into the blood. Interestingly, the concentration of bone alkaline phosphatase increases at the biological onset (i.e., the subclinical state) of rickets and is closely associated with rickets activity. In the present study, we found that bone alkaline phosphatase concentration was significantly elevated, which indicates an increased osteoblast activity, although serum calcium concentration did not significantly change, which likely indicates changes in the bone metabolism of women who are of childbearing age. Furthermore, vitamin D exhibited a significant negative correlation with bone alkaline phosphatase, but not with alkaline phosphatase, which indicates that bone alkaline phosphatase is a more sensitive indicator of bone metabolism.

Studies have demonstrated that 25OHD concentration is directly correlated with bone mineral density (BMD) in men and women.[12] Furthermore, Ying et al[13] found that vitamin D concentration was positively correlated with BMD in older postmenopausal women from downtown Beijing. Intestinal calcium absorption is also significantly lower when 25OHD concentration is ≤75 nmol/L, compared with the absorption when 25OHD concentrations are >75 nmol/L. In this context, PTH increases the renal tubular reabsorption of calcium, and the kidneys convert 25OHD into 1,25$(OH)_2$D. In addition, osteoblast activation drives the differentiation of osteoclasts into mature osteoclasts, which ultimately results in reduced bone mass and increased risks of osteoporosis and fracture. Bone ultrasonography is a simple and reliable method for measuring bone mass, and our findings revealed that vitamin D concentrations were positively correlated with bone ultrasonography findings, which is consistent with findings in the literature.

Improving vitamin D status among women who are of childbearing age

Vitamin D affects calcium and phosphorus metabolism and also plays various physiological roles that contribute to the maintenance of human health and cell growth and development. Thus, vitamin D concentration is closely associated with a variety of diseases, such as cardiovascular diseases, diabetes, immune diseases, neuromuscular disorders, renal diseases, skin diseases (e.g., psoriasis), and cancer. Zhuang et al[14] have reported that pregnant women and newborns in different regions of China have vitamin D in sufficiency, especially in spring, when there were moderate and positive correlations between maternal and neonatal 25-(OH)D concentrations. Therefore, the foetuses did not receive sufficient vitamin D from the uterus, which could result in the development of rickets.[15] Low vitamin D concentrations in women who are of childbearing age may result in low vitamin D concentration during pregnancy, especially if the pregnancy occurs during the winter. Furthermore, a study of vitamin D concentrations in pregnant women and newborns reported that Caucasians have a lower 25OHD concentration and a higher vitamin D concentration, compared with non-Caucasians. These values were significantly lower than those that have been reported in Europe[16] and Oceania,[17] although they were similar to the values that have been reported in the Middle East[18] and Asia (e.g., Turkey).[19] One possible explanation for the low serum vitamin D concentrations among Asian women is that Asian foods contain very little vitamin D, although this likely does not play a major role, given that the majority of vitamin D is derived via sunlight exposure. A second possible explanation is that Asian skin experiences increased pigmentation after exposure to sunlight, which might reduce the ability of the skin to produce vitamin D in response to ultraviolet exposure. A third possible explanation is that exposure to sunlight is reduced during the winter, due to the fewer hours of sunlight, less outdoor activity, and less skin exposure. Hollis et al[20] have reported that, regardless of race, vitamin D supplements (4,000 IU) are the most effective and safe method to achieve an adequate serum vitamin D concentration in mothers and their babies. However, as vitamin D concentration can vary according to each individual's sunlight exposure and diet, the doses of vitamin D supplements should be tailored accordingly, and further research is needed to examine whether women with a low vitamin D concentration should receive high-dose vitamin D supplements at the onset of pregnancy.

Limitations

This study has several important limitations that warrant consideration. First, our sample was relatively small and was derived from a single center, and these factors are associated with well-known risks of bias. Second, the questionnaire provided limited diet-related data for women of childbearing age, which limits any comprehensive comparison of the various parameters between the winter and summer. Third, we only examined healthy women who worked indoors in Beijing, which likely limits the extrapolation of our findings to a broader group of women. Thus, future studies should examine a broader patient population to provide a more comprehensive understanding of vitamin D status among healthy women who are of childbearing age. Fourth, we only performed bone ultrasonography testing during the summer and cannot comment on the women's bone metabolism status during winter (although we observed a lower vitamin D concentration during the winter). Therefore, larger studies with a broader patient population are needed to perform further analyses, and these studies should perform a more comprehensive evaluation of the participants' dietary intake of vitamin D and their sunlight exposure (e.g., adjust for clothing and/or the use of sunscreen). The results of those studies may provide more clear data regarding the cause of the low vitamin D concentration that we observed during the summer.

Conclusion

In conclusion, serum vitamin D deficiency was common among healthy women in Beijing who worked indoors and were of childbearing age, during both winter and summer. Furthermore, bone ultrasonography findings and serum concentrations of 25OHD, parathyroid hormone, and bone alkaline phosphatase accurately reflected the women's bone metabolism status. Therefore, we recommend that women who are of childbearing age should actively pursue outdoor activities (e.g., sun bathing), and increase their dietary intake of vitamin D, calcium, phosphorus, and protein, in order to achieve optimum bone metabolism status.

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AUTHOR DISCLOSURES

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