Optimal Vitamin D Status in a Middle-Aged and Elderly Population Residing in Shanghai, China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BEF 1 Qiqige Aleteng*
C 1 Lin Zhao*
E 1 Huandong Lin
D 1 Mingfeng Xia
E 1,2 Hui Ma
B 3 Jian Gao
D 4 Baishen Pan
AG 1 Xin Gao

1 Department of Endocrinology and Metabolism, ZhongShan Hospital, Fudan University, Shanghai, P.R. China
2 Department of Geriatrics, ZhongShan Hospital, Fudan University, Shanghai, P.R. China
3 Department of Clinical Nutrition, ZhongShan Hospital, Fudan University, Shanghai, P.R. China
4 Department of Laboratory Medicine, ZhongShan Hospital, Fudan University, Shanghai, P.R. China

Background: The aim of this study was to investigate the optimal vitamin D status in the middle-aged and elderly population residing in Shanghai, China.

Material/Methods: A total of 1,829 males and postmenopausal females older than 45 years of age in the Changfeng community of Shanghai were included in this study. The optimal vitamin D level was determined according to the suppression of parathyroid hormone (PTH) and the highest bone mineral density (BMD). Locally weighted scatter plot smoothing (LOWESS) was performed to study the correlations of 25(OH)D with PTH and BMD in the lumbar spine and total hip, adjusting for gender, age, weight, use of calcium and vitamin D supplements, eGFR, smoking status, and alcohol consumption.

Results: The mean serum 25(OH)D concentration was 48.0±19.2 nmol/L for the whole study population. The circulating PTH was maximally suppressed by the serum 25(OH)D of 55 nmol/L in the total population (60 nmol/L for males and 50 nmol/L for females). The 25(OH)D concentrations corresponding to the highest BMD at lumbar spine (L1–L4) and total hip were 53 nmol/L and 75 nmol/L, respectively, for the whole population. These values were also higher in males than females.

Conclusions: The optimal 25(OH)D concentration of 55 nmol/L is sufficient to maintain the bone health and metabolic status in middle-aged and elderly individuals living in Shanghai. Males probably need higher vitamin D concentration than females. There are differences between vitamin D status based on lumbar spine BMD and total hip BMD.

MeSH Keywords: Bone Density • Parathyroid Hormone • Vitamin D

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Background

Vitamin D is a well-known regulatory factor in calcium and phosphorus metabolism, which plays a critical role in bone and mineral homeostasis. Moreover, vitamin D has also been shown to exert extra-skeletal actions in addition to its classical roles. Vitamin D deficiency has been linked to many chronic illnesses, including common cancers [1], autoimmune diseases [2,3], infectious diseases [3], and cardiovascular diseases [4,5]. Therefore, in recent years, vitamin D has attracted increased attention. In fact, vitamin D deficiency is very prevalent among adults worldwide. Studies have reported that 20–100% of elderly men and women in the United States, Canada, and Europe suffer from vitamin D deficiency, with 25-hydroxyvitamin D [25(OH)D] less than 50 nmol/L [6–11]. In China, the prevalence rates of vitamin D deficiency [25(OH)D <50 nmol/L] and insufficiency [50≤ 25(OH)D <75 nmol/L] among middle-aged and elderly individuals have been reported to be 69.2% and 24.4%, respectively, indicating that only approximately 6% of this population has sufficient vitamin D levels [12].

Although the serum 25(OH)D level has been used to reflect a person's vitamin D status [6], there is still no consistent standard for the optimal vitamin D status. The optimal serum 25(OH)D level can be defined by several criteria, including the maximal suppression of circulating parathyroid hormone (PTH), greatest calcium absorption, highest bone mineral density (BMD), reduced bone loss rates, reduced falling rates, and reduced fracture rates [13]. Previous studies have reported that the serum 25(OH)D level with the greatest inhibiting effects on PTH levels varies from 30–99 nmol/L [14–17]. The Institute of Medicine (IOM) guidelines have recommended 50 nmol/L as adequate levels of 25(OH)D to achieve bone health in general population [18]. On the other hand, however, the Endocrine Society guidelines recommend a target 25(OH)D concentration of 75 nmol/L [19].

The cutoff point for optimal vitamin D status is influenced by many factors, such as the residential latitude, current season, as well as an individual's skin color, age, sex, genetics, renal function, mobility level, calcium intake, and phosphate and magnesium status [19,20]. Controversy persists regarding a standard cutoff point (such as 50 nmol/L or 75 nmol/L), because a single cutoff point may not be suitable for all populations (e.g., young versus old, and men versus women). Moreover, elevated standard cutoff point would lead to increased prevalence of vitamin D deficiency, which may result in aggressive treatment with vitamin D supplements in enlarged population and thereby increase the risk of vitamin D intoxication in some people.

It is well accepted that the middle-aged and elderly populations (> 45 years of age) are at high risk of vitamin D deficiency [21–24]. In this study, the vitamin D levels of residents greater than 45 years old from the Changfeng community of Shanghai, China, were investigated. According to these community-based data, chronic diseases among the middle-aged and elderly participants were also studied [25]. The optimal vitamin D levels in this population were determined based on the PTH levels combined with BMD, and a reference for the clinical treatment of vitamin D deficiency in adults living in Shanghai, China, was thereby provided.

Material and Methods

Study population

Consecutive numbering 2,223 males and females who were subjected to the vitamin D level detection, from May 2010 to June 2011, were initially screened. The exclusion criteria were as follows: primary hyperparathyroidism (n=3), Paget's disease (n=0), bone tumors (n=53), and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (n=265). There were 129 premenopausal females, who were also excluded. Finally, a total of 1,829 subjects were included in this study.

In the subgroup analysis, 184 healthy subjects were identified with normal bone mass (T score ≥−1.0 SD) and normal metabolic status, and some subjects were excluded, i.e., those with abnormal glucose metabolism (according to the American Diabetes Association 2010 criteria [22]), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, taking antihypertensive medications, and with diagnosed hypertension), metabolic syndrome (according to the diagnostic criteria of the International Diabetes Foundation published in 2005 [23]), overweight status (24 ≤BMI <28 kg/m^2), and obesity (BMI ≥28 kg/m^2; according to the diagnostic criteria of the 2003 Working Group on Obesity in China [24]). Interviews, physical examinations, and BMD scans were carried out at the Changfeng Community Health Service Center. The study was approved by the ethics committee of Zhongshan Hospital, Fudan University, and was conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Patient interviewing

All the included participants were interviewed by trained investigators using a standardized questionnaire, and the data regarding their medical history, medication history, and health-related behaviors (lifestyle habits) were obtained. Information regarding current drug usage that would affect vitamin D levels was also obtained from these participants, including calcium, vitamin D, and bisphosphonate.

Physical examination

Weight and height were measured for each patient. Body mass index (BMI) was calculated as the weight divided by the height squared (kg/m^2). Resting blood pressure was measured three times, and the mean value was used for analysis. Waist circumference was measured midway between the lowest rib margin and the iliac crest. Hip circumference was measured at the widest level over the greater trochanters.

Laboratory assessments

Blood samples were obtained from each patient after a fasting period of at least 10 hours. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), creatinine (Cr), and liver enzyme levels were measured using a Model 7600 Automated Bio-Analyser (Hitachi, Tokyo, Japan). Low density lipoprotein cholesterol (LDL-C) level was calculated using the Friedewald equation [26]. Fasting blood glucose (FBG) and 2-hour post-load plasma glucose (PPG) levels following a 75-g oral glucose challenge for participants without diabetes were measured with the glucose oxidase method.

Serum 25(OH)D and PTH levels were measured using a Roche Cobas E601 electro chemiluminescence system with complete reagents (Roche Diagnostics, Basel, Switzerland). Intra- and inter-batch variation coefficients for 25(OH)D and PTH were below 10% and 5%, respectively. The eGFR was estimated based on the serum Cr concentration using the Modification of MDRD formulation, i.e., eGFR ($mL/min/1.73~m^2$)=186×$Scr^{-1.154}$×$age^{-0.203}$×0.742 (if female)×1.233 (if Chinese) [27].

BMD measurement

All participants underwent BMD measurement at the lumbar spine (L1–L4) and the total hip, using a Lunar iDXA (GE Healthcare, Milwaukee, WI, USA). Data for BMD and T score were obtained for each patient.

Statistical analysis

Data were expressed as mean ±SD. Statistical analysis was performed using the SAS 9.2 software (Cary, NC, USA). Normally distributed continuous variables between male and female subjects were compared using independent-sample t test, while skewed variables were compared using the Mann-Whitney U-test.

Measurements for 25(OH)D and PTH levels were divided into the following four groups according to seasons: spring (March to May), summer (June to August), autumn (September to November), and winter (December to February). Differences among the seasons were tested by one-way analysis of variance (ANOVA), and post hoc comparison was performed with least squares difference test.

Locally weighted scatter plot smoothing (LOWESS) was performed to study the correlations of 25(OH)D with PTH and BMD in lumbar spine and total hip, adjusting for gender, age, weight, using of calcium and vitamin D supplements, eGFR, smoking status, and alcohol consumption. All statistical analyses were two tailed; $p<0.05$ was considered statistically significant.

Results

Basic information and clinical characteristics of participants

Totally 1,829 participants were finally analyzed in the study, including 845 males and 984 postmenopausal females. Basic information and clinical characteristics of these participants are listed in Table 1. The mean age of these participants was 64.2±9.9 years. In the subgroup analysis, the 25(OH)D levels were analyzed, with normal bone mass (n=1,179) and for healthy subjects (normal bone mass and normal metabolism status; n=184). Our results showed that the mean 25(OH)D level in these participants was 48.0±19.2 nmol/L. In particular, the mean 25(OH)D level for male patients (51.9±20.1 nmol/L) was significantly higher than the postmenopausal female participants (44.7±17.9 nmol/L) ($p<0.001$). Moreover, the prevalence of 25(OH)D level <50 nmol/L was 60.4% over the whole population, which was 90.7% for the prevalence of 25(OH)D level <75 nmol/L. On the other hand, the mean PTH level in male participants (40.1±17.1 pg/mL) was significantly lower than the postmenopausal participants (41.8±18.9 pg/mL) ($p=0.045$). In addition, the BMD at the lumbar spine for male participants (1.15±0.18 g/cm^2) was significantly higher than that the postmenopausal females (0.99±0.17 g/cm^2) ($p<0.001$). Similar results were obtained for the BMD at hip (0.86±0.13 and 0.77±0.15 g/cm^2 for male and postmenopausal female participants, respectively) ($p<0.001$).

Relationship between 25(OH)D and PTH levels

Relationship between the levels of 25(OH)D and PTH in the total population, males, and females was analyzed. As shown in Figure 1, the LOWESS plots showed an inverse relationship between the levels of 25(OH)D and PTH. However, no plateau was observed in the PTH level. Our results indicated that the circulating PTH concentration was maximally suppressed when the serum 25(OH)D was 55 nmol/L (Figure 1A) in all participants, 60 nmol/L in male participants (Figure 1B), and 50 nmol/L in female participants (Figure 1C), after adjusting for gender, age, weight, calcium, and vitamin D supplementation, eGFR, smoking status, and alcohol consumption.

Table 1. Basic information and clinical characteristics of study subject.

	Total	Male	Female	P
N	1829	845	984	–
Age (years)	64±10	64±10	64±10	0.600
Height (cm)	161.4±8.4	167.6±6.3	156.2±6.2	<0.001
Weight (kg)	63.5±10.8	68.6±9.8	59.2±9.6	<0.001
BMI (kg/m^2)	24.3±3.3	24.4±3.1	24.2±3.5	0.288
Waist (cm)	84.2±9.6	86.4±8.9	82.3±9.8	<0.001
Hips (cm)	93.4±7.2	93.8±6.5	93.0±7.7	0.024
SBP (mmHg)	137±20	138±19	136±20	0.079
DBP (mmHg)	77±11	79±11	76±11	<0.001
FBG (mmol/l)	5.6±1.6	5.7±1.8	5.4±1.3	<0.001
2hPBG (mmol/l)	7.7±3.4	7.8±3.7	7.7±3.2	0.284
TC (mmol/l)	5.1±0.9	4.8±0.9	5.4±0.9	<0.001
TG (mmol/l)	1.8±1.3	1.8±1.3	1.8±1.2	0.894
HDL-C (mmol/l)	1.4±0.4	1.3±0.3	1.5±0.4	<0.001
LDL-C (mmol/l)	2.9±0.8	2.8±0.7	3.1±0.8	<0.001
ALT (U/L)	19±14	20±12	19±16	0.048
AST (U/L)	21±9	22±7	21±10	0.657
Cr (μmol/l)	68±15	78±12	59±9	<0.001
eGFR (ml/min/1.73 m^2)	97±19	95±19	98±20	0.003
25(OH)D (nmol/l)	48.0±19.2	51.9±20.1	44.7±17.9	<0.001
PTH (pg/ml)	41.0±18.1	40.1±17.1	41.8±18.9	0.045
BMD at lumbar spine (g/cm^2)	1.06±0.19	1.15±0.18	0.99±0.17	<0.001
BMD at total hip (g/cm2)	0.82±0.15	0.86±0.13	0.77±0.15	<0.001
25(OH)D <50 nmmol/l (%)	60.4%	52.4%	67.3%	<0.001
25(OH) <75 nmmol/l (%)	90.7%	86.6%	94.1%	<0.001

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBG – fasting blood glucose; 2hPBG – 2-hour postprandial blood glucose; TC – total cholesterol; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; PTH – parathyroid hormone; BMD – bone mineral density; ALT – alanine aminotransferase; AST – aspartate aminotransferase; Cr – creatinine; eGFR – estimated glomerular filtration rate.

Relationship between 25(OH)D and BMD levels

BMD measurements for the lumbar spine (L1–L4) and total hip were analyzed separately. Our results demonstrated that the highest BMD at the lumbar spine occurred at the serum 25(OH)D concentration of 53 nmol/L for the overall study population (Figure 2A), while this concentration was 60 nmol/L for the male participants (Figure 2B) and 48 nmol/L for the postmenopausal females (Figure 2C), after adjusting for gender, age, weight, calcium, and vitamin D supplementation, eGFR, smoking status, and alcohol consumption. The highest BMD at the

hip occurred at the serum 25(OH)D concentration of 75 nmol/L for the overall study population (Figure 3A), while the concentrations were 86 nmol/L and 66 nmol/L for males (Figure 3B) and postmenopausal females (Figure 3C), respectively, also after adjusting for the confounding factors aforementioned.

25(OH)D levels in subjects with normal bone mass and normal metabolism status

To further explore the optimal 25(OH)D level, 1,179 participants with normal bone mass (T score ≥–1.0) (721 males

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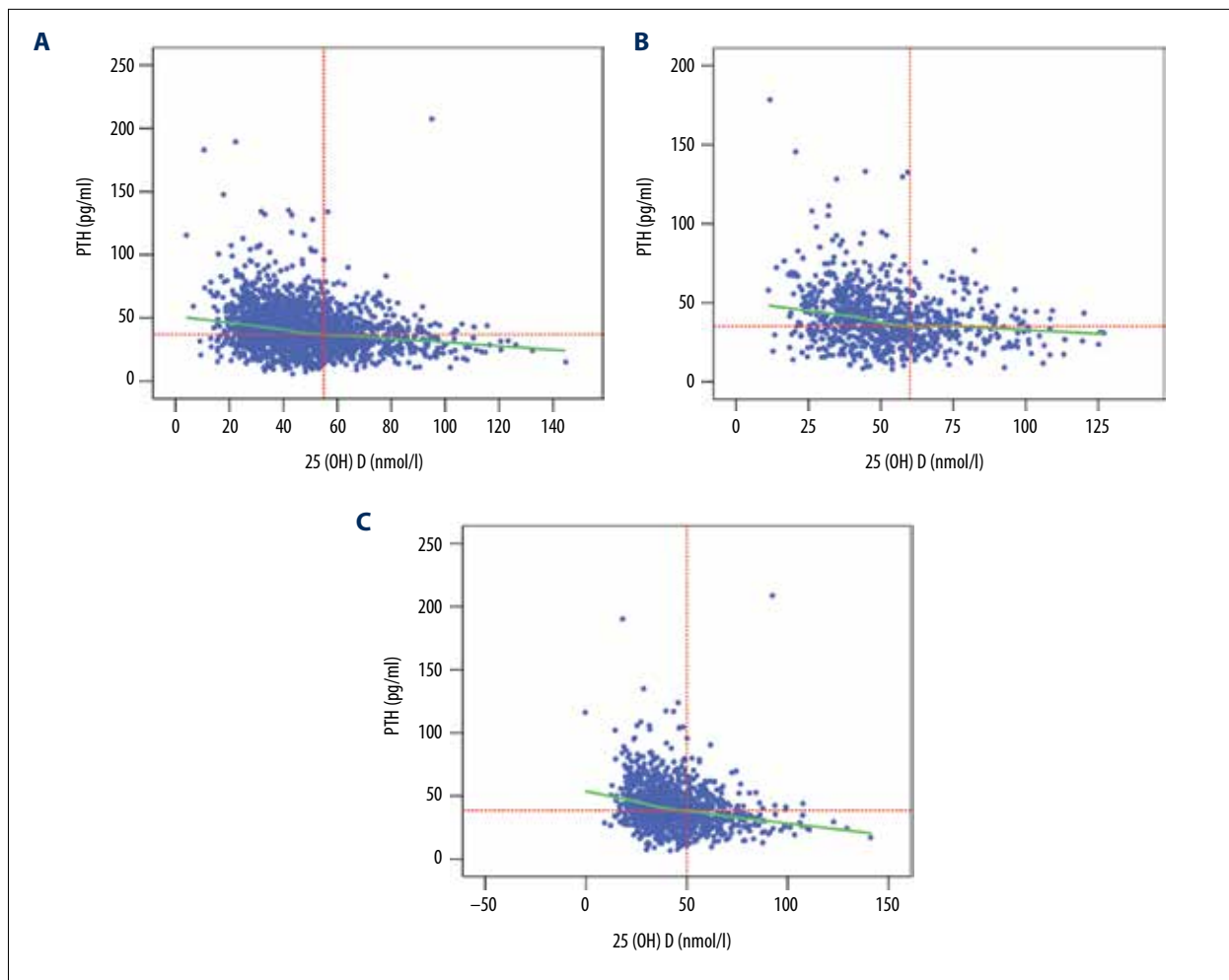
Figure 1. LOWESS plots for circulating PTH and serum 25(OH)D levels. (**A**) All study participants. (**B**) Males. (**C**) Females.

and 458 postmenopausal females) were identified. As shown in Table 2, the mean 25(OH)D level in the population was 49.1±19.1 nmol/L. Moreover, the mean 25(OH)D level in male participants (51.9±20.1 nmol/L) was higher than postmeno-pausal female subjects (44.6±16.6 nmol/L) ($p<0.001$).

On the other hand, 184 healthy participants with normal bone mass and normal metabolic status were identified, excluding those with abnormal glucose metabolism (according to the American Diabetes Association 2010 criteria [28]), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, use of antihypertensive medications, and diagnosed hypertension), metabolic syndrome (according to the diagnos-tic criteria of the International Diabetes Foundation published in 2005 [29]), overweight status (24≤ BMI <28 kg/m²), and obe-sity (BMI ≥28 kg/m²; according to the diagnostic criteria of the 2003 Working Group on Obesity in China [30]). In this group, the mean 25(OH)D level was 49.7±20.2 nmol/L. Moreover, the mean 25(OH)D level in male participants (52.5±23.3 nmol/L)

was marginally higher than postmenopausal female subjects (47.0±16.3 nmol/L) (p=0.064) (Figure 4A).

Analysis of 25(OH)D levels for different seasons

The 25(OH)D levels in different seasons were then investigat-ed. Our results showed that the mean 25(OH)D levels in the spring, summer, autumn, and winter for the whole study pop-ulation were 43.4±16.3, 49.6±22.0, 54.3±18.5, and 47.0±18.2 nmol/L, respectively. Moreover, the 25(OH)D levels were higher in summer and fall compared to winter and spring ($p<0.001$). This trend also was observed for both genders (Figure 4B).

Discussion

The significance of vitamin D has been emphasized in pub-lic health contexts because vitamin D deficiency, which is in-dependently associated with an increased risk of mortali-ty in the general population [31], is a great threat to elderly
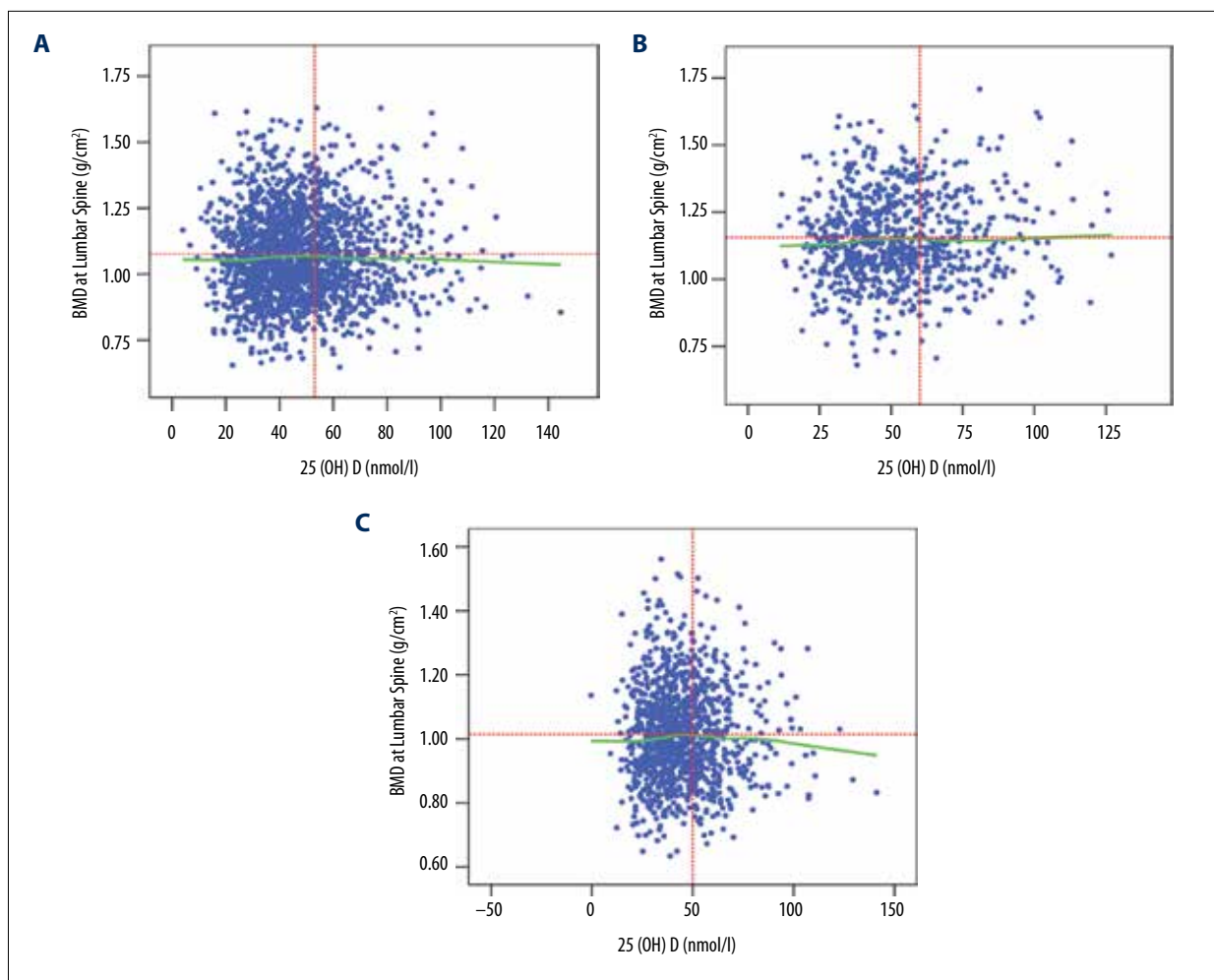
Figure 2. LOWESS plots for BMD in the lumbar spine and serum 25(OH)D levels. (**A**) All participants. (**B**) Males. (**C**) Females.

people [32,33]. Previous studies have reported that vitamin D deficiency is related to a higher risk of metabolic bone diseases, cancers [1], autoimmune diseases [2,3], infectious diseases [3], and cardiovascular diseases [4,5]. However, the optimal vitamin D level for bone health is still controversial.

In this cross-sectional study, vitamin D deficiency is highly prevalent in the middle-aged and elderly population from Shanghai, China, especially in the postmenopausal females. The optimal vitamin D status for bone health in a population greater than 45 years of age in Shanghai were explored, and the relationship between serum vitamin D and PTH levels combined with BMD measurements at the lumbar spine (L1–L4) was investigated. Our results indicated that the optimal 25(OH)D level was 55 nmol/L for the overall population, 60 nmol/L for males, and 50 nmol/L for postmenopausal females. Therefore, male participants in this age range likely needed higher vitamin D concentration than female participants to achieve the same BMD level. The optimal cutoff point value of 55 nmol/L for the whole study population was determined

based on the relationship between vitamin D and PTH concentrations, which was close to the level recommended by the IOM guidelines (50 nmol/L) [18], however lower than the target of 75 nmol/L recommended by the Endocrine Society guidelines [19]. In order to maintain the vitamin D-related metabolic balance, the maximal suppression of circulating PTH means not only the greatest calcium absorption, but also the synthesis and metabolic balance of vitamin D (i.e., the balance between synthetic pathways mediated by PTH and degradative pathways mediated by fibroblast growth factor-23, FGF-23). Alshayeb et al. [27] have found that raising the serum 25(OH)D levels with cholecalciferol treatment to above 50 nmol/L could also increase the degradation of 25(OH)D [34]. Therefore, they suggest that the 25(OH)D level of 50 nmol/L is sufficient for maintaining bone health, and the target of 75 nmol/L is relatively too high. Sai et al. [35] defined vitamin D insufficiency as the serum 25(OH)D concentration below 75 nmol/L based on serum PTH suppression, however this result was not supported by a literature review of 70 studies. Therefore, they conclude that vitamin D insufficiency should be redefined as
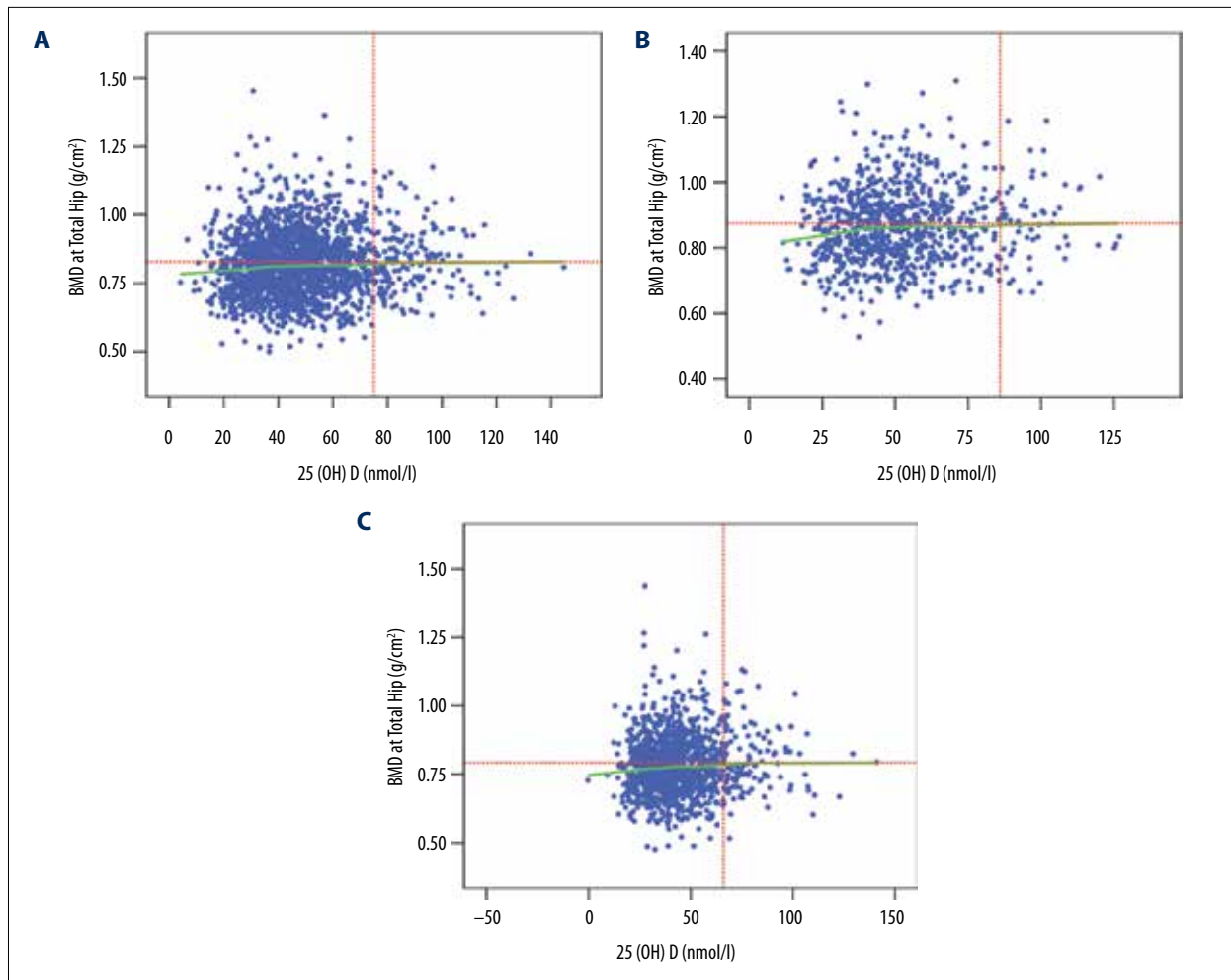
Figure 3. LOWESS plots for BMD in the total hip and serum 25(OH)D levels. (**A**) All participants. (**B**) Males. (**C**) Females.

the serum 25(OH)D concentration below 50 nmol/L. In addition, Nakamura et al. [36] investigated the cutoff point of serum 25(OH)D concentration in relation to elevated serum PTH concentrations in 582 elderly Japanese women. The study concluded that the serum 25(OH)D for elderly Japanese women should be maintained at 40 nmol/L or higher.

The relationship between the serum 25(OH)D concentration and BMD was also investigated. BMD is a noninvasive and effective way to evaluate bone health, and therefore has been considered as another way to estimate the optimal 25(OH)D level. It is well accepted that lower vitamin D levels are associated with bone health problem (e.g., increased risks of fractures and falls) [19,37]. Moreover, previous studies have shown that addition of vitamin D to calcium supplementation has long-term beneficial effects on BMD in the elderly [38-39]. Our data indicated a similar 25(OH)D concentration optimal to achieve the highest BMD in the lumbar spine (L1–L4) and maximal suppression of circulating PTH (53 nmol/L and 55 nmol/L, respectively) in the overall study population. To further

explore the optimal 25(OH)D level in the middle-aged to elderly population, 1,179 participants with normal bone mass were analyzed. In this population, the mean level of 25(OH)D was 49.1±19.1 nmol/L, indicating the 25(OH)D level of 50 nmol/L, which basically met the demand for bone health. In a previously study concerning 320 elderly females with an average age of 77.2±4.6 years and mean 25(OH)D level of 44.3±12.9 nmol/L, Zhu et al. [40] found that the vitamin D supplementation added no extra short-term skeletal benefit superior to the calcium citrate supplementation. Similarly, Aloi et al. [41] conducted a study regarding 208 healthy black postmenopausal females aged 50–75 years old with the mean 25(OH)D level of 47 nmol/L, and they did not observed any effect of vitamin D3 supplementation on bone loss or bone turnover markers. These results indicated that increasing the 25(OH)D level to greater than 50 nmol/L might not improve bone health and the level of 50 nmol/L would be suitable for maintaining bone health in elderly people.

Table 2. Basic information and clinical characteristics of subpopulation with normal BMD.

	Total	Men	Women	P
N	1179	721	458	–
Age (years)	64±10	64±10	62±9	<0.001
Height (cm)	163.8±7.9	167.9±6.1	157.5±5.9	<0.001
Weight (kg)	66.6±10.2	69.7±9.4	61.9±9.6	<0.001
BMI (kg/m^2)	24.8±3.2	24.7±3.0	24.9±3.5	0.235
Waist (cm)	85.7±9.3	87.1±8.6	83.5±9.9	<0.001
Hips (cm)	94.3±7.0	94.3±6.2	94.4±8.0	0.915
SBP (mmHg)	137±19	139±19	135±19	0.004
DBP (mmHg)	78±11	80±11	76±11	<0.001
FBG (mmol/l)	5.6±1.7	5.8±1.9	5.5±1.3	0.001
2hPBG (mmol/l)	7.8±3.5	7.9±3.7	7.7±3.2	0.478
TC (mmol/l)	5.0±0.9	4.8±0.9	5.3±0.9	<0.001
TG (mmol/l)	1.9±1.4	1.8±1.3	1.9±1.5	0.101
HDL-C (mmol/l)	1.3±0.3	1.2±0.3	1.4±0.3	<0.001
LDL-C (mmol/l)	2.8±0.8	2.7±0.8	3.0±0.8	<0.001
ALT (U/L)	20±12	20±12	20±12	0.540
AST (U/L)	21±7	21±7	21±7	0.874
Cr (μmol/l)	71±15	79±12	60±10	<0.001
eGFR (ml/min/1.73 m^2)	96±19	95±18	98±20	0.013
25(OH)D (nmol/l)	49.1±19.1	51.9±20.1	44.6±16.6	<0.001
PTH (pg/ml)	40.0±16.4	40.0±17.1	40.0±15.3	0.952
BMD at lumbar spine (g/cm^2)	1.17±0.14	1.19±0.15	1.13±0.11	<0.001
BMD at total hip (g/cm2)	0.87±0.14	0.88±0.12	0.85±0.16	<0.001
25(OH)D <50 nmmol/l (%)	58.6%	52.9%	67.5%	<0.001
25(OH) <75 nmmol/l (%)	90.1%	86.6%	95.4%	<0.001

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBG – fasting blood glucose; 2hPBG – 2-hour postprandial blood glucose; TC – total cholesterol; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; PTH – parathyroid hormone; BMD – bone mineral density; ALT – alanine aminotransferase; AST – aspartate aminotransferase; Cr – creatinine; eGFR – estimated glomerular filtration rate.

Increasing evidence has indicated the extra skeletal health effects of vitamin D, such as effects on the immune system, infectious diseases, autoimmune diseases, diabetes, cardiovascular disease, and cancers [33,34]. To exclude the potential confounding factors related to the extra skeletal effects of vitamin D, 184 healthy participants with normal bone mass and normal metabolic status were further analyzed. Interestingly, the mean 25(OH)D level in this subgroup was 49.7±20.2 nmol/L, which was close to 50 nmol/L. Thus, the reasonable 25(OH)D level for healthy population would be approximately 50 nmol/L.

It seems that the 25(OH)D level of 50 nmol/L is sufficient for maintaining the basic metabolic health [35,36].

Interestingly, our results showed that the 25(OH)D level corresponding to the highest BMD in the lumbar spine (L1–L4) was basically equivalent to that associated with the maximal suppression of circulating PTH. However, the 25(OH)D level corresponding to the highest BMD in the total hip was 75 nmol/L, which was significantly higher than the lumbar spine (L1–L4). A recent study examined 675 iliac crest biopsies from German
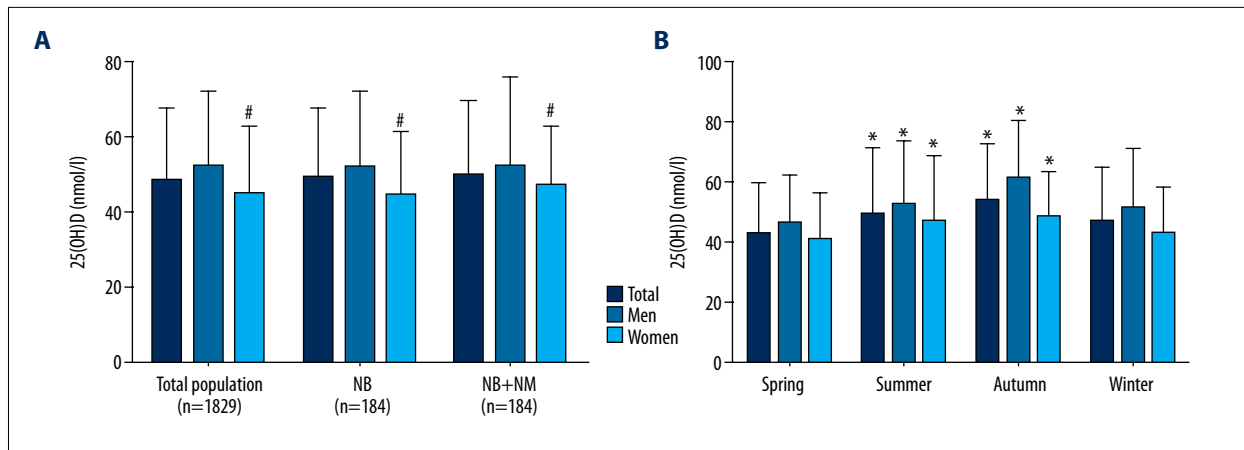
Figure 4. Analysis of the mean 25(OH)D levels in participants. (**A**) Mean 25(OH)D levels in different subgroups according to health status. Compared with males, # $p<0.001$. (**B**) Mean 25(OH)D levels in different seasons. Compared with spring, * $p<0.001$. NB – normal bone mass; NB+NM – normal bone mass and normal metabolism status.

adults (401 males, mean age of 58.2 years; and 270 females, mean age of 68.2 years) for structural histomorphometric parameters. They have concluded that the dose of vitamin D supplementation should ensure that the circulating levels of 25(OH)D reach a minimum threshold of 75 nmol/L to maintain the skeletal health [42]. In this study, the same sites of the participants were examined, and consistent conclusion was addressed. Thus, there might be differences between vitamin D status based on lumbar spine BMD and total hip BMD. In order to improve the hip BMD, the circulating levels of 25(OH)D needed to be increased to above 75 nmol/L. A previous study reported that vitamin D status may be less related to the BMD of the total hip compared with that of the lumbar spine [43]. Moreover, another study found that vitamin D supplementation increases BMD to a lesser extent in the total hip than the lumbar spine [44]. These differences may be caused by the fact that other mechanical factors (i.e., physical activity and weight) would exert greater effects on the total hip BMD than on the lumbar spine BMD. Moreover, sex hormone deficiency has also been shown to make the lumbar spine more susceptible to vitamin D insufficiency [43].

Our results indicated that the optimal vitamin D level in males was significantly higher than the postmenopausal females, which was consistent with previous findings [20]. In another study 4,276 people (1,926 males and 2,350 females), aged 40 years and younger were selected from 16 administrative districts of South Korea [45]. The study showed that there are gender-dependent skeletal effects in this population, and thus serum 25(OH)D level should be maintained higher in males to ensure BMD [45]. Moreover, a previous study reported gender-based differences in the serum 25(OH)D and glycemic measurements [46]. Vitamin D deficiency is associated with reduced insulin production in participants with type 2 diabetes, which is mainly observed in males. In line with this, our results suggested

that, compared with females, males might need higher circulating levels of vitamin D to maintain the same BMD and normal metabolic state. The underlying mechanism is not entirely clear. Some studies have indicated that males have lower fat content than females with the same BMI, which means less vitamin D is stored in fat and more stays in the blood after cutaneous synthesis [47,48]. In addition, previous studies showed that lower 25(OH)D concentrations were associated with lower SHBG levels and higher free testosterone levels in both males and females, and lower estradiol and higher DHEA levels in females, independent of adiposity and lifestyle. But there was no significant association between 25(OH)D and total testosterone in males [49,50]. Therefore, the difference of sex hormone may also represent an important factor for the different vitamin D status in females and males. The sex hormones and lifestyle were not addressed in the present study. Further in-depth studies are still needed to determine whether vitamin D supplementation influences the sex hormone levels. Shanghai is located on the eastern coast of China at subtropical latitude of 31°N. The city experiences four distinct seasons. Compared with summer and autumn, the vitamin D levels in our study population were lower in winter and spring. Vitamin D synthesis in the skin is mediated by ultraviolet B irradiation (290–315 nm). The effect of the short wavelength would be diminished by changes in the zenith angle over the year, which might lead to reduced vitamin D synthesis mediated by ultraviolet radiation [19,51]

There are also some limitations about our study. First, the adults under the age of 45 years or premenopausal females were not included. Second, our study population resided only in Shanghai, which does not represent the entire nation. Further studies are still needed in other regions. Third, the potential reasons for the differences in circulating vitamin D levels and the actually physiological requirement for vitamin D are still

needed to be studied. In addition, detailed information about exercise and diet of the participants was absent.

Conclusions

In summary, in this study, the optimal vitamin D status in middle-aged and elderly individuals in terms of different vitamin D functions and different health status were investigated. Our results indicated that the optimal 25(OH)D level for the whole population was 55 nmol/L. Moreover, the optimal vitamin D status based on lumbar spine BMD was more reliable than that based on total hip BMD. Furthermore, males likely need more vitamin D than females to maintain normal BMD and metabolic state. Our findings provide valuable reference for the treatment of vitamin D deficiency among middle-aged and elderly people in Shanghai, China.

Conflict of interest

None.

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