Original Article

Maintenance vitamin D3 dosage requirements in Chinese women with post menopausal osteoporosis living in the tropics

Yogeswari Venugopal MBBS, MRCP, Sharifah F Wan Muhamad Hatta MBChB, MMed, MRCP, Nurbazlin Musa BSc, Siti Abdul Rahman BSc, Jeyakantha Ratnasingam MD, Mmed, Sharmila Sunita Paramasivam MD, MRCP, Lee Ling Lim MBBS, MRCP, Luqman Ibrahim MBBS, Mmed, Karen Choong MD, Alexander TB Tan MBChB, MRCP, Karuthan Chinna BSc, MSc, PhD, Siew Pheng Chan MBBS, MRCP, Shireene R Vethakkan MBBS, MMed, MD

Department of Medicine, University of Malaya, Lembah Pantai,59100 Kuala Lumpur,Malaysia

Background and Objectives: Vitamin D3 (cholecalciferol) dose required to maintain sufficiency in non-Caucasian women with postmenopausal osteoporosis (PMO) inthe tropics has not been well studied. Some guidelines mandate 800-1000 IU vitamin D/day but the Endocrine Society (US) advocates 1500-2000 IU/day to maintain 25-hydroxyvitamin-D (25(OH)D) concentration at >75 nmol/L. We aimed to establish oral cholecalciferol dose required to maintain 25(OH)D concentration at >75 nmol/L in PMO Chinese Malaysian women, postulating lower dose requirements amongst light-skinned subjects in the tropics. **Methods and Study Design:** 90 Chinese Malaysian PMO women in Kuala Lumpur, Malaysia (2°30'N) with baseline serum 25(OH)D levels ≥50 nmol/L were recruited. Prior vitamin D supplements were discontinued and subjects randomized to oral cholecalciferol 25,000 IU/4-weekly (Group-A) or 50,000 IU/4-weekly (Group- B) for 16 weeks, administered under direct observation. Serum 25(OH)D, PTH, serum/urinary calcium were measured at baseline, 8 and 16 weeks. **Results:** Baseline characteristics, including osteoporosis severity, sun exposure (~3 hours/week), and serum 25(OH)D did not differ between treatment arms. After 16 weeks, 91% of women sufficient at baseline, remained sufficient on 25,000 IU/4-weekly compared with 97% on 50,000 IU/4-weekly with mean serum 25(OH)D 108.1±20.4 and 114.7±18.4 SD nmol/L respectively (p=0.273). At trial's end, 39% and 80% of insufficient women at baseline attained sufficiency in Group A and Group B (p=0.057). Neither dose was associated with hyperparathyroidism or toxicity. **Conclusions**: Despite pretrial vitamin D supplementation and adequate sun exposure, 25.6% Chinese Malaysian PMO women were vitamin D insufficient indicating sunshine alone cannot ensure sufficiency in the tropics. Both ~900 IU/day and ~1800 IU/day cholecalciferol can safely maintain vitamin D sufficiency in >90% of Chinese Malaysian PMO women. Higher doses are required with baseline concentration <75 nmol/L.

Key Words: vitamin D, oral cholecalciferol, postmenopausal osteoporosis, Chinese ethnicity, tropical

INTRODUCTION

Osteoporosis and its associated morbidity/mortality is a major public-health issue in the rapidly aging demographic of East and Southeast-Asia.[1] Subjects of Chinese ethnicity are especially vulnerable to osteoporosis as corroborated by the fact that hip-fracture incidence in Malaysian women >age 50 years is highest amongst those of Chinese descent.[2]

Vitamin D supplementation, coupled with antiresorptive therapy and adequate calcium intake, form the cornerstones of postmenopausal osteoporosis (PMO) management. Vitamin-D plays an important role in calcium metabolism, bone health and muscle strength.[3] Cholecalciferol supplementation reduces fracture risk and increases lower extremity strength, however these effects have been shown to be dose dependent. 80-90% of vitamin-D is derived from cutaneous synthesis upon sun exposure, while 10-20% is obtained from dietary sources.[4]

Hypovitaminosis D is a global problem affecting both northern and even more southern latitude populations. Vitamin D inadequacy (<75 nmol/L) has been demonstrated in 52% of a large cohort of North American PMO women despite active osteoporosis treatment.[5] In recent times, evi dence of prevalent vitamin D inadequacy

Corresponding Author: Dr Yogeswari Venugopal, Endocrine Division, Medical Department, Penang General Hospital, Jalan Residensi, 10990 Georgetown, Penang, Malaysia.
Tel: +6012-5072452; Fax:603-79556936
Email: yogesvenugopal@gmail.com; theyoges@hotmail.com
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has also emerged in sun rich areas such as Hawaii, Saudi Arabia and Southern India.[6,7] Studies have also documented widespread vitamin-D inadequacy in China[8] and amongst South Korean/Japanese PMO women(some of whom were already vitamin D supplemented).[9]

Vitamin D inadequacy is also prevalent in tropical equatorial Malaysia, with evidence of ethnicity and sun exposure being important predictive factors. There have been only 4 published studies examining serum 25(OH)D levels amongst women in Malaysia and Singapore, two Southeast Asian countries with large immigrant Chinese populations and year long sunshine. Only of one of these studies investigated women with confirmed PMO. Lips et al[10] reported a 0% prevalence rate of vitamin D deficiency amongst a mixed population of women confirmed to have PMO - both vitamin D supplemented and unsupplemented, living in Singapore (a majority-Chinese population). Amongst pre-menopausal women who did not receive vitamin-D supplementation in Kuala Lumpur, Green et al[6] found a lower rate of vitamin D deficiency amongst the Chinese (38%) compared with Malays (74%). Echoing these findings of an apparent ethnic 'protection' from vitamin D deficiency amongst Chinese in a tropical setting, Rahman et al[11] evaluating vitamin D supplement naïve postmenopausal women discovered a high prevalence of vitamin D deficiency (<50 nmol/L)(71%) amongst those of Malay ethnicity and ~6-fold lower prevalence (11%) amongst urban Chinese. It is not known, however, if these women had PMO as their BMD was not assessed. On the other hand, a Malaysian study by Musa et al[12] found that 81.3% of an urban population of perimenopausal Chinese women (52.3% total population) without osteoporosis, despite minimal sunscreen use had vitamin D levels <50 nmol/L compared with 11.9% of a rural population of predominantly Malay women (84%); with the main factor predictive of deficiency being reduced sun exposure amongst urban women.

Many osteoporosis guidelines[13-16] mandate a minimum of 800-1000 IU/day vitamin D as an essential component of osteoporosis therapy. There is less clarity when it comes to what the optimal serum 25(OH)D concentration is and how much vitamin D is required to maintain an optimal concentration. While it is well established that a high dose vitamin D loading regimen is required as initial treatment of vitamin-D deficiency (<50 nmol/L) in order to attain a concentration of >75 nmol/L,[14,17] there has been little scientific inquiry into the dose of cholecalciferol required to maintain serum concentrations of >75 nmol/L in non-Caucasian subjects living in the tropics, where sun exposure, cultural practices and skin pigmentation may differ. Neither is there agreement on the definition of vitamin D sufficiency with some researchers targeting concentrations of serum 25(OH)D of >50 nmol/L and others aiming for >75 nmol/L. The IOM (Institute of Medicine) 2010 guidelines,[18] aiming for a lower serum 25(OH)D target of >50 nmol/L, advocate maintenance doses of 600 IU/day in post-menopausal women aged 51-70 years and 800 IU/day for those aged >70. These recommendations were made allowing for minimal sun exposure and were meant for healthy subjects, i.e. those without osteoporosis.[18] In contrast, the Endocrine Society 2011 guidelines[17] state that maintenance doses up to 1500-2000 IU/day may be required to attain the higher optimal target of >75 nmol/L 'in those at risk of vitamin D deficiency and falls/fractures based on high quality evidence'. This threshold serum vitamin-D concentration of 75 nmol/L is recommended based on the fact that secondary hyperparathyroidism is usually seen with concentration of <75 nmol/L (but not above), and that fractional absorption of calcium does not increase with vitamin D supplementation in subjects with concentrations of >75 nmol/L.[16] Similarly, the 2010 Canadian guidelines[15] while recommending a minimum of 800 IU vitamin-D/day for treatment of osteoporosis have a caveat that >1000 IU/day may be required to attain optimal vitamin D status. The 2013 UK National Osteoporosis Society Practical Guideline[14] on the other hand, in accord with the IOM, considers serum 25(OH)D concentration above 50 nmol/L as being within the optimal range and advocates treatment of those with osteoporosis (and vitamin-D deficiency) on potent antiresorptives with a maintenance dose of 800-2000 IU/day, making allowances for dark skinned populations and those with religious/cultural dress-codes limiting sun exposure.

Very few interventional studies focusing on the appropriate dose of vitamin D required to maintain sufficiency have been conducted in East-Asian/Oriental subjects with PMO at high risk of fracture. Neither can results of studies in Japan, Korea and China[19] be extrapolated to immigrant Chinese living in equatorial Southeast Asia where climate and diet differ. It is possible that Chinese women in Malaysia having more sun exposure than their northern Oriental counterparts and Caucasians may require lower supplementary vitamin D doses to maintain adequacy. However, the effect of age on the skin's ability to synthesize vitamin D and cultural practices such as sun-avoidance may confound the aging PMO Chinese woman's ability to maintain serum 25(OH)D >75 nmol/L.

Our study focuses on determining the maintenance dose of vitamin D supplementation in women at high risk of fracture i.e. PMO Chinese women. Knowing that a minimum of 800 IU of vitamin-D[17,20,21] can prevent both falls/fractures, regardless of vitamin D status, from studies in Caucasian populations of postmenopausal women and that 700-1000 IU/day may maintain concentrations of >75 nmol/L in 50% of the Caucasian population,[21] we therefore designed a prospective randomized controlled trial comparing the ability of a low (~900 IU/daily) and high (~1800 IU/daily) maintenance dose of oral cholecalciferol (vitamin D3) to sustain serum concentrations of >75 nmol/L amongst community dwelling Chinese women with PMO living in Kuala Lumpur, Malaysia which is located 2° 30'N, postulating that a lower dose of ~900 IU daily would be required amongst this light skinned ethnic group living in a tropical climate with year-long sunshine.

SUBJECTS AND METHOD

A total of 142 community dwelling Chinese Malaysian women with postmenopausal osteoporosis, over the age of 55, attending University of Malaya Medical Centre Osteoporosis Clinic in Kuala Lumpur, Malaysia (2°30' N) with baseline serum vitamin D concentrations of >50 nmol/L were invited to participate in the study. 90 women who met the inclusion criteria were recruited (Figure 1).

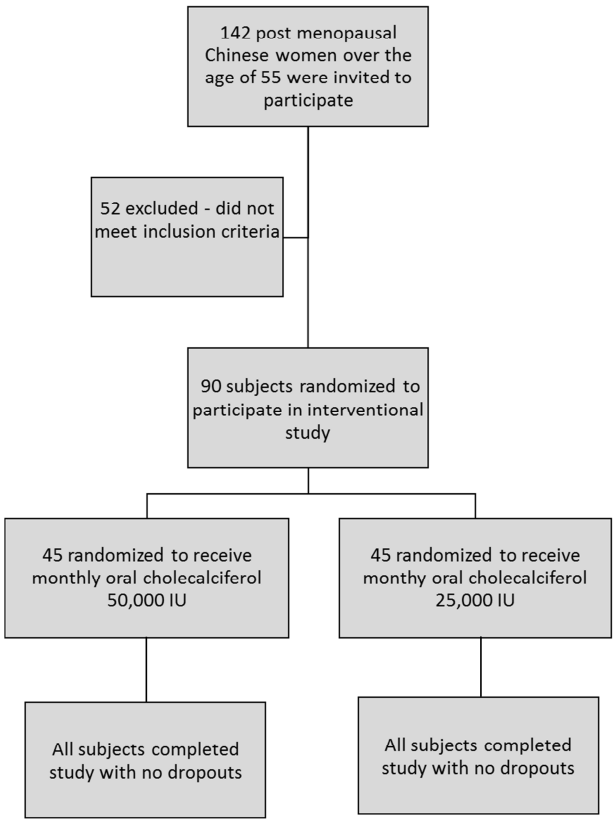

Figure 1. Patient flow diagram

We excluded patients with: malabsorption (prior history of colectomy, Roux-en-Y gastric-bypass), known metabolic disease other than PMO and secondary osteoporosis (granulomatous diseases, thyrotoxicosis, glucocorticoid-induced osteoporosis, liver/renal disease). Patients on over-the-counter vitamin D supplements and medications that affect vitamin D metabolism (rifampicin, estrogen, glucocorticoids, anticonvulsants) were also excluded. Participants agreed to refrain from using sunscreen, altering dietary calcium intake and sun exposure or from taking self prescribed calcium or vitamin D supplements during the study. This study was approved by an institutional review board and signed informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Subjects had a baseline screening visit with serum 25(OH)D level measurement, followed by an initial randomization visit and then visits at 4, 8, 12 and 16 weeks after randomization. Baseline laboratory tests included renal and liver function tests and serum calcium, phosphorus, 25-(OH)D, intact PTH, and albumin levels with 24 hour urinary calcium measurements. All relevant data were obtained via an interview, physical examination and questionnaire as well as from medical records. Patients were administered a validated sun exposure questionnaire[22] and degree of skin pigmentation was quantified using Von Luschan's Skin Colour Chart.[23] Study subjects' baseline characteristics are summarized in Table 1.

At the second visit, eligible patients with serum vitamin D concentrations of >50 nmol/L had their previous vitamin D supplements discontinued and were block randomized to either receive 50,000 IU oral cholecalciferol (vitamin D3) or 25,000 IU every 4 weeks for 16 weeks. Serum 25(OH)D levels, serum calcium, phosphorus, serum intact PTH, serum albumin levels and 24 hour urinary calcium measurements were evaluated once again at 8 and 16 weeks post-randomization. Any concomitant medications or adverse events were recorded at 4-weekly visits.

Oral cholecalciferol was ingested monthly under direct supervision during study visits. Each dose of cholecalciferol was diluted in 200 ml of water. The cholecalciferol used in this study was formulated as spray dried powder stabilized with DL-alpha tocopherol (dry vitamin D3 100 SD/S)(DSM Nutritional Products Switzerland Ltd). All subjects were also assigned to receive 1 g of calcium carbonate daily.

Definitions

Vitamin D deficiency is defined as serum 25(OH)D concentration of <50 nmol/L, insufficiency as serum 25(OH)D of 50-<75 nmol/L, sufficiency as 75-250 nmol/L and vitamin D intoxication as serum 25(OH)D concentrations exceeding 250 nmol/L.[17] Secondary hyperparathyroidism is defined as normal serum calcium with a PTH above upper limit of normal (>6.8 pmol/L).

Osteoporosis is defined as one of the following: bone mineral density(BMD) T score <-2.5 at any site or written documentation of diagnosed osteoporosis in medical chart or low trauma, non-pathological fragility fracture of the hip, spine, wrist, humerus or clavicle after age 45, on

Table 1. Baseline characteristics[†]

Baseline Parameters		Total vitamin D concentration		*p* value
		<30 ng/mL, n=23	≥30 ng/mL, n=67	
Age, years	Mean±SD	66.5±6.4	68.1±5.5	0.263
BMI, kg/m^2	Mean±SD	22.7±2.8	22.8±3.8	0.965
Vitamin dose at baseline, IU	Mean±SD	361±326	539±375	0.046
PTH, pmol/L	Mean±SD	4.90±2.12	4.53±1.67	0.395
Fraction of BSA exposed, %	Median (IQR)	0.37 (0.21-0.45)	0.39 (0.26-0.45)	0.725
Hours of sun exposure per week, hours	Median (IQR)	2.50 (1.25-4.33)	2.25 (1.17-4.50)	0.828
Skin colour	Median (IQR)	26.0 (24.0-26.0)	26.0 (24.0-26.0)	0.708
Sun Exposure Index (SEI)[‡]	Median (IQR)	0.93 (0.35-1.95)	0.79 (0.37-1.58)	0.831

SD : Standard Deviation, IQR : Interquartile Range, BSA : Body Surface Area.
[†]Data is expressed as mean±SD and median (Interquartile range) depending on normality.
Reference laboratory ranges are as follows: 25(OH)D, 3–70 ng/mL; iPTH, 1.6–6.8 pmol/L; Serum Ca, 2.12 mmol/L–2.52 mmol/L; 24 hour urinary Ca, 1.0–8.8 mmol/24 hours.
[‡]Sun Exposure Index (SEI)=mean body surface area x total exposure hours per week.

Table 2. Baseline characteristics after randomization[†]

Baseline characteristics	Group A Patients receiving 25,000 IU vitamin D monthly (n=45)	Group B Patients receiving 50,000 IU vitamin D monthly (n=45)	*p* value
Age (years)	68±5	67±6	0.586
Years after menopause	17±8	17±7	0.937
Age at menopause (years)	51±4	50±4	0.560
Height (cm)	154±5	153±6	0.587
Weight (kg)	53.5±8.9	53.2±9.0	0.867
BMI (kg/m^2)	22.9±3.7	22.6±3.4	0.651
Vitamin D intake <400 IU /day	10 (22.2)	13 (28.9)	0.733
Vitamin D intake ≥400-<800 IU /day	21 (46.7)	18 (40.0)	
Vitamin D intake ≥800 IU /day	14 (31.1)	14 (31.1)	
BMD spine (g/cm^2)	0.823±0.116	0.848±0.135	0.348
T score spine	-2.7±0.8	-2.5±0.9	0.338
BMD neck of femur (g/cm^2)	0.697±0.099	0.694±0.104	0.880
T score neck of femur	-2.1±0.8	-2.2±0.8	0.364
BMD total hip (g/cm^2)	0.803±0.139	0.763±0.096	0.115
T score total hip	-1.8±1.1	-2.0±0.8	0.160
Patients with falls	16 (35.6)	23 (51.1)	0.136
Patients with previous fractures	16 (35.6)	23 (51.1)	0.136
Serum corrected calcium (mmol/L)	2.26±0.10	2.30±0.13	0.142
Serum albumin (g/L)	40.9±2.7	40.8±2.5	0.841
Baseline 25(OH) D level (nmol/L)	90.2±23.1	91.2±24.6	0.788
iPTH level (pmol/L)	4.7±1.8	4.6±1.8	0.856
24 hour urine calcium (mmol/24 hours)	4.26±2.40	3.66±2.31	0.230
Skin colour[‡]	25.1±1.9	24.6±2.0	0.201
Sun Exposure Index[§]	1.22±1.32	1.15±1.13	0.803
Mean sun exposure (total hours/week)	3.00±2.91	3.20±2.64	0.728
Mean body surface area (m^2)	0.36±0.13	0.34±0.11	0.423

Data is expressed as mean±SD. Comparison of indices between subjects in group (A) and group (B) were done with the Student's t test or Mann–Whitney test depending on normality. Figures in brackets represent percentage of population in each group.
[†]Reference laboratory ranges are as follows: 25(OH)D, 7.5–175.0 nmol/L; iPTH, 1.6–6.8 pmol/L; serum Ca, 2.12 mmol/L–2.52 mmol/L; 24 hour urinary Ca, 1.0–8.8 mmol/24 hours
[‡]Measured using Von Lushchan Skin Colour Chart.
[§]Sun Exposure Index (SEI)=mean body surface area x mean sun exposure.

current or previous treatment for osteoporosis with any approved osteoporosis medication.[9] Prior to study enrolment, patients had their bone mineral densities evaluated by DXA [DPX IQ 240 GE device/Lunar Prodigy device (GE Medical Systems Lunar, Madison, WI, USA)].

Biochemistry

Serum 25(OH)D concentration was measured by an electro-chemiluminescence immunoassay (ECLIA) from Roche Diagnostics (minimum detectable concentration: 7.5 nmol/L, maximum: 175.0 nmol/L). Intra assay precision (coefficient of variation): mean of 38.4 nmol/L-6.9%, mean of 169.5 nmol/L-1.7%. Inter assay variability: mean of 38.8 nmol/L-12.2%, mean of 169.5 nmol/L-2.2%.

Serum PTH was measured by the Elecsys analyzer using ECLIA for quantitative determination of intact PTH in serum (minimum detectable level: 0.1 pmol/L, maximum: 52.5 pmol/L). Intra-assay precision: mean of 2.1 pmol/L-4.1%, mean of 6.1 pmol/L-2.2%. Inter-assay variability: mean of 2.1 pmol/L-6.2%, mean of 6.1 pmol/L-4.1%. The reference range for serum PTH is 1.6-6.8 pmol/L.

Serum and urinary calcium were measured by O-cresolphthalein complex using automated equipment [Dimension Vista (Siemens)].

Statistical analysis

Statistical Analysis was performed using SPSS 16.0J for Windows. Descriptive statistics are reported as mean ± SD. Baseline comparisons were analyzed using Student's *t* test or Mann–Whitney test depending on normality. A one-way between groups, analysis of covariance (ANCOVA) was conducted to compare effects of oral cholecalciferol supplementation. *p* value <0.05 was consideredstatistically significant.

RESULTS

Baseline characteristics

90 community dwelling Malaysian women of Chinese ethnicity with post menopausal osteoporosis were enrolled in this study. 82.2% of women were already on some form of vitamin D supplementation (dose 200-1200 IU/day) prior to study enrolment which was ceased on recruitment. At baseline, 42.2% of subjects were on 400 IU daily and 31.1% on >800 IU daily. 80% of the sample population were on active treatment for osteoporosis with either alendronate or strontium. 45 subjects each were randomized to receive either 25,000 IU (Group-A) or 50,000 IU (Group-B) oral cholecalciferol every 4 weeks respectively. No significant differences were present at baseline between the 2 groups with regards to age, BMI, duration of menopause, severity of osteoporosis, sun exposure, skin colour, mean serum 25(OH)D, serum calci-

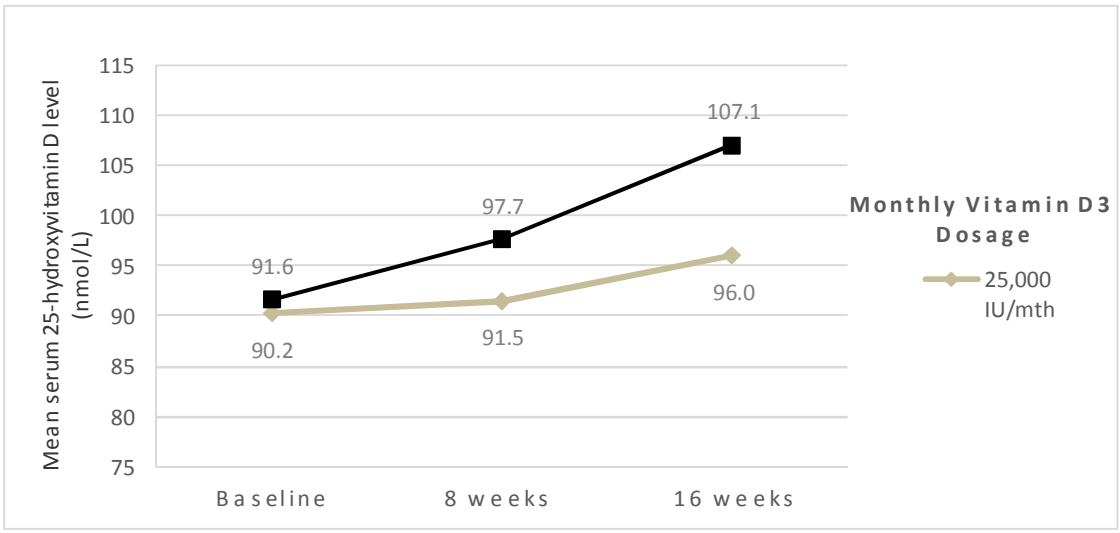

Figure 2. Serum 25-hydroxyvitamin D concentrations for all groups at all study time points. Effect of monthly cholecalciferol supplementation on serum 25(OH)D. After 16 weeks of supplementation, serum 25(OH)D increased to a greater extent from baseline with 50,000 IU/month compared to 25,000 IU/month with a mean level of 107.1±22.7 nmol/L from a level of 91.6±24.6 nmol/L in patients receiving 50,000 IU monthly oral cholecalciferol with an increment of 15.6±16.3 nmol/L ($p \leq 0.001$) compared to a mean 25(OH)D level of 96.0±24.1 nmol/L from a baseline level of 90.2±23.1 nmol/L with an increment of 5.8±16.0 nmol/L ($p=0.019$) in patients taking 25,000 oral chocecalciferol monthly.

um, and 24 hour urinary calcium levels (Table 2). At baseline, 25.6% of the total 90 subjects had 25(OH)D concentrations between 50.1-74.9 nmol/L (insufficiency) (n=23) and 74.4% had concentration of >75 nmol/L (sufficiency). At baseline, 82.6% and 82.1% of insufficient and sufficient subjects respectively had received vitamin D supplementation prior to study enrolment. Median vitamin D dose was significantly lower in the insufficient group at baseline compared with the sufficient group. 13% vs 37.3% of subjects were on >800 IU/day prior to study enrolment in the insufficient and sufficient at baseline subgroups respectively. There was no significant difference in sun exposure between the insufficient and sufficient subgroups at baseline with both spending a median of 2.5 and 2.25 hours/week in the sun, respectively. (Table 1) Neither were there significant differences in age, BMI and sun exposure index between the insufficient and sufficient subgroups (data not shown). Mean concentration of serum 25(OH)D in both the sufficient and insufficient subcategories did not differ significantly in either treatment arm (Table 3).

Vitamin D status after treatment with monthly cholecalciferol

Mean serum 25(OH)D concentrations rose significantly from baseline to 16 weeks in both treatment groups, Group A: 90.2±23.1 to 96.0±24.1 SD nmol/L, Group B 91.6±24.6 to 107.1±22.7 SD nmol/L (Figure 2). After 16 weeks of oral cholecalciferol supplementation, in women who were already sufficient at baseline, 91% remained sufficient on 25,000 IU 4-weekly (low-dose therapy) while 97% of those on 50,000 IU 4-weekly (high-dose therapy) remained sufficient. These differences were not clinically significant. The drop in vitamin-D sufficiency rate from 100% at baseline, to 91% and 97% in Group A and B, respectively, after 4 months was also not clinically significant ($p=0.273$). Only 39% (5/13 women) and 80% (8/10 women) of those who were insufficient at baseline however attained sufficiency in Group A (low dose) and Group B (high dose), respectively - these differences however only approached clinical significance ($p=0.057$).

In the sample population as a whole, there were no significant differences in mean serum 25(OH)D concentrations between the low dose and high dose therapy groups at 8 weeks, however at 16 weeks the mean vitamin D concentration in patients taking high dose monthly vitamin D was significantly higher ($p=0.027$). Amongst women with insufficient vitamin D concentrations at the start of the trial[serum 25(OH)D level: 50 -<75 nmol/L], treatment with low-dose vitamin D (Group-A) produced a significant increase in serum 25(OH)D concentration only after 16 weeks therapy, whereas treatment with high dose (Group B) produced significant increments at both 8 and 16 weeks. In those who were sufficient at baseline, low dose therapy produced no significant change in serum 25(OH)D at 8 or 16 weeks compared with baseline but high dose cholecalciferol produced significant increases at both time points.

PTH suppression

All patients were normocalcemic at baseline and end of study. At baseline, 15.6% and 8.9% of participants in the low dose (Group-A) and high dose (Group B) arms, respectively, had secondary hyperparathyroidism. All participants with secondary hyperparathyroidism attained serum PTH values within the normal range after 4 months treatment. Mean PTH levels were not significantly different between the vitamin D insufficient and sufficient at baseline subgroups respectively (4.9±2.1 vs 4.5±1.7 pmol/L, $p=0.395$). PTH levels declined significantly in both treatment arms with vitamin D therapy (Figure 3). There was no significant difference in mean PTH levels between both treatment arms at any time point.

Table 3. Change in Vitamin D Concentration from Baseline after oral cholecalciferol supplementation

Monthly vitamin D dosage	Mean 25-OH D concentration (nmol/L)										
	All patients (vitamin D ≥50 nmol/L)			Insufficient at baseline (50-<75nmol/L)				Sufficient at baseline (≥75nmol/L)			
	Baseline	8 weeks	16 weeks	Baseline	8 weeks	16 weeks	Subjects achieving vitamin D sufficiency (%)	Baseline	8 weeks	16 weeks	Subjects maintaining vitamin D sufficiency (%)
Gp A 25.000 IU/mth	90.2±23.1	91.5±23.5	96.0±24.1	62.6±7.6	66.6±10.8	72.3±13.7	39	101±17.0	102±19.3	106±20.4	91
Gp B 50,000 IU/mth	91.6±24.6	97.7±21.6*	107±22.7*	60.1±5.9	72.3±10.4	80.4±14.8	80	101±20.0	105±18.2*	115±18.4*	97

Data is expressed as mean±SD.
*p<0.05 (significant change in serum 25(OH)D concentration compared to baseline).
No statistically significant difference in changes in serum 25(OH)D concentration between Group A and B.

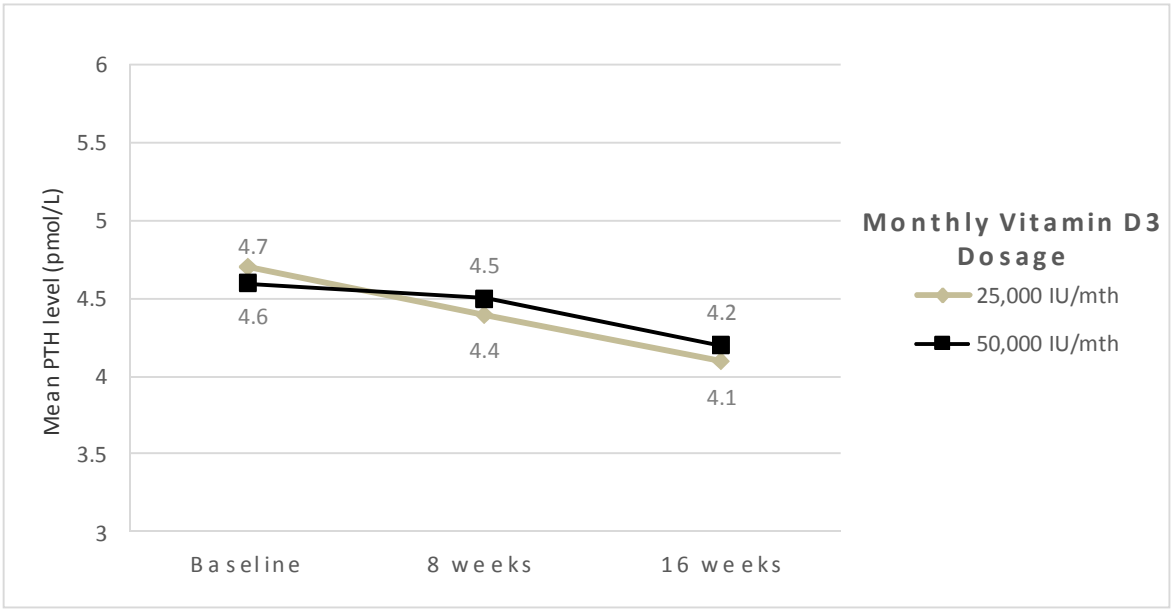

Figure 3. Effect of monthly cholecalciferol supplementation on serum PTH levels. Effect of monthly cholecalciferol supplementation on serum PTH concentration. No significant difference between the concentration of PTH supression in any groups at any time point. The mean PTH concentration at 6 months is less than baseline PTH concentration after 16 weeks of supplementation. Serum PTH decreased by 0.5±2.4 pmol/L (p=0.154) to reach mean value of 4.1±1.7 pmol/L from a baseline value of 4.7±1.8 pmol/L in subjects receiving 25,000 IU cholecalciferol monthly. Subjects receiving 50,000 IU cholecalciferol had a decline in PTH concentration of 0.4±1.6 pmol/L(p=0.108) from a baseline concentration of 4.6±1.8 pmol/L to reach the concentration of 4.2±1.2 pmol/L.

Safety

None of the subjects developed hypercalcemia or hypercalciuria during the course of this study. There were no significant differences in corrected serum calcium or urinary calcium excretion between treatment groups.

DISCUSSION

Unexpectedly, a quarter of our cohort of Chinese-Malaysian women with PMO had evidence of vitamin D insufficiency (50-<75 nmol/L) at baseline despite the fact ~80% were vitamin D supplemented. Conversely, only a small proportion of those sufficient at baseline (17.9%) were not cholecalciferol-supplemented prior to study enrolment. In comparison with women who were sufficient at baseline, the insufficient subgroup was on significantly lower doses of vitamin D i.e. only 13% were on >800 IU/day compared with the sufficient subgroup, 37.1% of whom were on >800 IU/day. Those who were insufficient at baseline also had a median of 2.5 hours of sun-exposure/week which was not significantly different from those who were sufficient at baseline. These findings indicate that sun exposure and diet alone are insufficient to maintain adequate vitamin D concentrations in this high fracture risk patient cohort of Chinese ethnicity. Ethical concerns precluded a placebo arm in our study, given the fact that many guidelines advocate a minimum vitamin-D dose of 800 IU/day as one of the cornerstones of osteoporosis therapy.[13-16,20] There are several reasons substantiating universal vitamin D supplementation in the elderly PMO woman: (1) Vitamin D therapy prevents falls and fractures in the elderly regardless of vitamin D status. (2) Most RCTs demonstrating efficacy of active osteoporosis therapy have done so in combination with calcium and vitamin D supplementation. (3) The assumption (evidenced by our cohort) that vitamin D inadequacy is prevalent in the elderly.[13,20] Indeed the fact that a significant proportion of our cohort were insufficient at baseline, despite vitamin D supplementation indicates that it is not a question of whether vitamin-D supplementation is required but rather how much vitamin D is necessary for optimal bone health amongst the Chinese diaspora to Southeast Asia.

We also found that a maintenance dose of 25,000 IU cholecalciferol (vitamin D3) monthly for 16 weeks, which is equivalent to ~900 IU/day, is as efficacious as a dose of 50,000 IU monthly (~1800 IU/day) in maintaining serum 25(OH) D concentrations above 75 nmol/L (vitamin D sufficiency) in the majority of Chinese Malaysian women (>90%) with postmenopausal osteoporosis(PMO) who are already sufficient at baseline with no significant differences in PTH suppression. 16 weeks on the low dose regimen however cannot normalize vitamin D concentration in Chinese Malaysian PMO women with serum 25(OH)D concentrations between 50-<75 nmol/L (vitamin D insufficiency), despite adequate sun exposure of 2.5 hours/week. In the total study population, although mean serum 25(OH)D concentrations after 16 weeks therapy was significantly higher in patients enrolled in the high dose arm, both dosing regimens resulted in average serum 25(OH)D concentrations either within or marginally above the 90-100 nmol/L range which has been associated with optimal bone health outcomes such as fracture reduction, improved BMD and improved lower extremity function.[21] Importantly after 16 weeks therapy, there were no patients with secondary hyperparathyroidism in both the low dose and high dose arms. Both the low dose and high dose maintenance regimes were safe with no cases of hypercalciuria, hypercalcemia or vitamin D intoxication in either arm.

To our knowledge, this is the first published study comparing low dose and high dose vitamin D supplementation amongst Chinese immigrants to tropical Southeast Asia. These findings indicate that 900 IU/day of vitamin D may be sufficient to maintain sufficiency in most Chinese PMO women living in equatorial Malaysia who already have serum 25 (OH) D concentration of >75 nmol/L. Based on good evidence in Western populations that the threshold levels for fracture risk reduction and fall prevention are 400 IU and 700-1000 IU, respectively,[18] a maintenance dose of 900 IU daily may be presumed to not only maintain sufficiency in Chinese Malaysian women but also improve bone-health related clinical endpoints. It is important to remember however that our study participants were prohibited from using sunscreen. It is therefore possible that Chinese Malaysian women who use sun block may require doses higher than 900 IU/day to maintain sufficiency.

Women with vitamin D insufficiency (50-<75 nmol/L) at baseline however may require doses as high as 1800 IU daily or a high dose loading regimen similar to that advocated by the Endocrine Society for treatment of vitamin-D deficiency i.e. 50,000 IU weekly for 8 weeks,[17] followed by a low dose maintenance regimen of 900 IU daily. Only 39% of women enrolled who were insufficient at baseline, attained sufficiency (>75 nmol/L) after 16 weeks of low dose therapy compared with 80% in the high-dose treatment group. These differences in rates of attaining vitamin D sufficiency approached clinical significance (p=0.057) and might have attained statistical significance if the sample size had been larger. It is possible, however, that a longer period of treatment with low dose vitamin-D3 900 IU/day extending up to perhaps 6 months may have been able to attain 25 (OH)D concentrations exceeding 30 ng/ml in these women, given that serum 25(OH)D continued to climb even in the latter half of this 16-week trial.

Others have also found that baseline serum 25(OH) D impacts on post treatment vitamin D concentrations and that lower maintenance doses can suffice in those with higher baseline levels. A review by Bischoff-Ferrari et al quotes evidence that optimal fracture prevention occurs in trials with mean achieved levels of ~100 nmol/L which were attained in subjects where 700-800 IU/day was administered to subjects with mean baseline concentrations between 43.9-76.9 nmol/L.[21] Trials in elderly postmenopausal Caucasian women living in Switzerland[24] and Boston, USA[25] in long-stay geriatric care/nursing home facilities have shown that while vitamin D doses of 800 IU daily + calcium can reduce falls, these patients who started with baseline concentrations <50 nmol/L were unable to achieve mean serum 25(OH)D concentrations >75 nmol/L after 12 weeks and 5 months treatment under trial conditions, respectively. On the other hand Chapuy et al[20] in their landmark RCT of 3,270 healthy ambulant com-

munity-dwelling elderly postmenopausal women (mean age: 84 years) which demonstrated vitamin D supplementation (+ calcium) reduced fractures, found that in a subgroup of 142 subjects in whom serum vitamin D was measured, 800 IU daily increased serum 25(OH)D from a baseline <50 nmol/L to levels of 100 nmol/L at 6 months, maintaining concentrations at 105 nmol/L at 12 and 18 months, respectively. These conflicting results of randomized placebo controlled trials in older Caucasian women living in northern latitudes seem to indicate that 800 IU/day is an adequate dose to maintain vitamin D sufficiency in ambulant subjects who may have the added benefit of sun-exposure, but is not efficacious in institutionalized subjects.

Baseline vitamin D is also known to be influenced by latitude/sun-exposure amongst other factors,[21] therefore it is entirely plausible that our cohort of light skinned Chinese PMO women living close to the equator with baseline vitamin D concentrations of >75 nmol/L, require a lower maintenance dose of vitamin D. The strength of our study design is that patient compliance was assured, as all vitamin D was administered in hospital under direct observation. Our study is limited by the lack of detailed diet history with regards to fish, mushroom and egg intake (important natural sources of dietary vitamin D).[17] However, as vitamin D fortified foods and fatty fish such as sardines, tuna and salmon are not widely available or consumed in Malaysia, this data may not have added much further information. It may also have been beneficial to assess the efficacy and safety of the two different maintenance doses over a longer time-frame of 6-12 months instead of 4 months.

These findings indicate that vitamin D therapy should be tailored to ethnic, geographical and cultural differences given the impact of these factors upon sun exposure and diet. It is not surprising that light skinned Chinese women in tropical Malaysia with year-long abundant sun exposure require lower doses of vitamin-D compared with Caucasians living in northern latitudes subject to seasonal variation in UVB radiation. However, given the fact that dermal production of vitamin-D upon sun exposure is compromised in the elderly,[4] these results were not a foregone conclusion. In addition, Asian culture has a propensity to prize fair complexioned women and this may thus have necessitated higher doses of supplemental vitamin D secondary to sun avoidance behaviour in our study population. Conversely, other studies seem to indicate that dark skinned Asian Indians and African Americans require higher than normal doses of vitamin D to correct vitamin D deficiency because of reduced UVB radiation penetration secondary to increased melanin pigmentation.[26,27] Our findings indicate that that the 2011 Endocrine Society recommendations that 1500-2000 IU vitamin D3/day may be necessary to raise serum 25(OH)D concentration above 75 nmol/L[17] may not be applicable in Chinese Malaysian women who are already vitamin D sufficient. Importantly, these results indicate that just as higher cholecalciferol doses are recommended in patients with obesity and those on anticonvulsants[17] perhaps lower maintenance doses can suffice in light skinned individuals living in the tropics.

In conclusion, despite pre-trial vitamin D supplementation and adequate sun exposure, 25.6% of Chinese Malaysian PMO women were vitamin D insufficient; indicating a need for cholecalciferol dose titration studies in this high fracture risk population. Our findings that both ~900 IU/day and ~1800 IU/day Vitamin-D3 can safely maintain serum 25(OH)D above 75nmol/L and suppress PTH in >90% of Chinese Malaysian women with postmenopausal osteoporosis who had vitamin D concentrations exceeding 75 nmol/L at baseline, have important public health consequences in Southeast Asia. These results highlight the need for location specific dosing studies amongst different ethnic groups in this era of patient centered treatment algorithms. Further studies examining long-term effects vitamin D dose on falls and fractures in Chinese immigrants living in South east Asia are warranted.

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AUTHOR DISCLOSURES

The authors have no conflicts of interests and have nothing to declare. This trial was funded by an independent investigator initiated grant funded by the University of Malaya Medical Centre.

ETHICAL APPROVAL

The design of this study was approved by the institutional review board and local ethical committee of the University of Malaya. Written and signed consent was obtained from all patients in accordance with the Declaration of Helsinki.

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