Prevalence and Risk Factors for Hypovitaminosis D among Healthy Adolescents in Kota Bharu, Kelantan

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Abstract

Objective. We aim to study the prevalence and risk factors of hypovitaminosis D among healthy adolescents in Kota Bharu, Kelantan based on the most recent Paediatric Consensus guideline.

Methodology. Ten public schools were selected from Kota Bharu, Kelantan. We analysed their demography (age, gender, ethnicity, income), measured their anthropometry (height, weight, BMI) and finally analysed their vitamin D and intact-Parathyroid hormone levels.

Results. The prevalence of hypovitaminosis D was 16.9% among healthy teenagers with mean age of 15.9±1.39 years. Multivariate analysis showed female gender (adjusted OR, 95% CI): 23.7 (5.64, 100.3) and Chinese 0.24 (0.07, 0.84) were the significant predictors for hypovitaminosis D.

Conclusion. The prevalence of healthy adolescents with hypovitaminosis D in Kota Bharu, Kelantan was 16.9% using the most recent cut off value of 30 nmol/L from the global consensus 2016. Female and Chinese were the significant risk factors associated with hypovitaminosis D. Higher cut off value would result in overestimation of prevalence rate of hypovitaminosis D.

Key words: hypovitaminosis D, adolescents, nutritional rickets

INTRODUCTION

Hypovitaminosis D or vitamin D deficiency is a cause of nutritional rickets. Rickets is due to defective bone mineralization in growing children. Vitamin D plays a major role in calcium regulation and as calcium is the main mineral in the bones, deficiency of vitamin D would lead to failure to absorb calcium and therefore it results in poor bone mineralization or rickets. Vitamin D deficiency during teenage years compromise bone mass and put teenagers at risk of adverse consequences of skeletal health; and there is also increase in likelihood of other medical problems in the future such as diabetes, hypertension, metabolic syndrome and certain cancers such as colorectal cancer. The prevalence of vitamin D deficiency worldwide varies widely depending on the definition used in the trials. It can be as low as 0.4% in China and as high as 86% in Middle East if it is based on the definition of vitamin D level <30 nmol/L. With higher cut off used, the reported prevalence ranged from 5-99%. Global consensus 2016 recommendations on prevention and management of nutritional rickets has defined vitamin D deficiency using <30 nmol/L as the critical cut off below which nutritional rickets is more likely to occur. This definition is consistent with that of The Institute of Medicine (IOM). Malaysian Health and Adolescents Longitudinal Research Team Study (MyHeARTs) reported the prevalence of vitamin D deficiency was 33% among adolescents with mean age of 15 years old from Selangor, Perak and the capital of Malaysia, Kuala Lumpur. However, the definition was based on higher cut off or adult value of 50 nmol/L. Eighty percent of the source of vitamin D is from skin synthesis following exposure to sun light. UVB from the sunlight would convert 7-dehydrocholesterol in the skin to cholecalciferol which will later be hydroxylated to inactive vitamin D in the liver then active vitamin D in the kidney. Any factors that may interfere with skin synthesis related to sociodemographic factors would lead to vitamin D deficiency. Any diseases that would affect liver, kidney and gut would also impair synthesis of vitamin D since liver and kidney are involved in the steps for hydroxylation of vitamin D while gut is the site at which active vitamin D and parathyroid hormone act to increase calcium and oral vitamin D absorption from the food. Known risk factors associated with vitamin D deficiency are poor sunlight exposure, sunscreen usage, darker skin, poor diet, older age, clothing, obesity, female gender and geographical location away from equator. The purpose of this trial was to investigate the prevalence of vitamin D deficiency using the most recent definition from the 2016 Global consensus in Kelantan which is one of the poorest states in Malaysia, and to study factors associated with vitamin D deficiency. Healthy adolescents were selected...
as teenage years is marked by the highest bone mineral accrual and if they do not have the optimal storage of vitamin D, they are more likely to face all detrimental effects of hypovitaminosis D as an adult.\textsuperscript{34}

**METHODOLOGY**

**Sampling design**
There were 45 public secondary schools in Kota Bharu based on the list provided by the Kelantan State Education. It was decided that ten schools were sufficient in order to recruit the required sample size. Participants were selected via nonprobability sampling. Specifically, students were recruited via purposive sampling. With the assistance and supervision of the teachers in charge, an invitation to participate were given to students in class who met the inclusion criteria. The students who expressed their interest were invited for a briefing by the primary research team.

**Research tool**
Subjects who gave consent, were asked to fill in the questionnaires to explore about sociodemographic factors. Height and weight were measured using standardized instruments and methods. Blood for 25-(OH)Vit D, intact-PTH were taken in EDTA tubes, centrifuged and stored at -80 degree centigrade. Vitamin D was analysed using Elecsys Vitamin D Cobas that utilised Electro Chemiluminescent Immunoassay for the quantitative measurement of total vitamin D. The Elecsys Vitamin D demonstrated good overall performance with a precision testing that showed within-run coefficient of variations (CVs) of <7%, within-laboratory CVs of 9.5%, between-laboratory precision CVs of <10.1% and a functional sensitivity below 9.8 nmol/L (at CV 12.9%).

**Inclusion and exclusion**
Healthy adolescents with age from 13-18 years old, without major medical problems such as kidney, liver and gut diseases were included. The information with regard to the health status and intake of vitamin D supplements were answered by parents in the questionnaire. Those who were on vitamin D supplements and had incomplete data entry were excluded.

**Statistical analysis**
Data analysis was performed using SPSS (IBM) version 22. Numerical data (age, weight, height, vitamin D, I-PTH) were expressed as mean and standard deviation while categorical data (gender, race, BMI) were presented as number and percentage. Simple and multiple logistic regression were applied to study the factors that affect vitamin D deficiency.

The prevalence of vitamin D deficiency was determined using a single proportion formula at confidence level/z =95% or 1.96, margin of error at 5%/ standard value of 0.05 and an estimated prevalence from Perez-Lopez et al., Jan 2010= 28%. By using the formula, a sample of 310 subjects was required to obtain a 95% confidence interval of 5% around a prevalence estimate of 20% and in order to allow for an expected 20% drop out rate (62), a total of 372 students were needed. Sample size for calculating factors associated with hypovitaminosis D was calculated with Pocock’s formula for comparing two proportions. Both numerical and categorical data were selected for the analysis of factors associated with hypovitaminosis D in the binary logistic regression with hypovitaminosis D as the dependent variable or outcome. From the results of simple logistic regression, selected variables / independent variables that have p value <0.25 were included in the multiple logistic regression. As for the multiple logistic regression analysis, we used forward and backward LR initially and it was decided to use the output of backward LR for the presentation of the final results.

**Ethical Approval**
The study was approved by the University Ethical Board with its reference USM/PPP/Ethics Com. 2012(60)

**RESULTS**
A total of 361 healthy adolescents with the mean age (SD); 15.9±1.39 years, age range (13-18 years) were recruited from 10 public schools in Kota Bharu, Kelantan. The predominant race was Malay, 307 (85%) while 54 (15%) were Chinese students. Female subjects outnumbered male with 227 (62.9%) vs 134 (37.1%). The mean vitamin D level was 19.62 ng/mL, 95% CI (18.77, 20.47) with interval estimates 19.62±0.8466. The average vitamin D level lies between 18.7 and 20.46 ng/mL. The prevalence of hypovitaminosis D / vitamin D deficiency based on the definition of <30 nmol/L, or 12 ng/mL was 16.3%. The mean weight and height (SD) were 53.0±16.8 kg, 156.2±19.2 cm. The mean (SD) of vitamin D level and intact-PTH were 19.6±8.2 ng/mL and 33.4±18.0 pmol/L respectively (Table 1).

**Table 1. Demographics of participants**

| Variable     | Results          |
|-------------|------------------|
| Age (years)* | 15.9±1.39        |
| Gender*     |                  |
| Male        | 134 (37.1)       |
| Female      | 227 (62.9)       |
| Weight (kg)*| 53.0±16.8        |
| Height (cm)*| 156.2±19.2       |
| Vitamin D (ng/mL)* | 19.6±8.2 |
| i-PTH (pmol/L)* | 33.4±18.0 |
| Race*       |                  |
| Malay       | 307 (85)         |
| Chinese     | 54 (15)          |
| BMI*        |                  |
| Obese       | 27 (7.5)         |
| Normal      | 292 (80.9)       |
| Underweight | 40 (11.1)        |

Significant factors associated with vitamin D deficiency after univariate analysis were older age, crude OR (95% CI); 0.87 (0.72, 1.06), female gender; 22.1 (5.30, 92.3), Malay; 3.79 (1.14, 12.59), family income <RM 2000; 4.32 (1.12, 16.59) and obesity; 2.74 (1.16, 6.49) (Table 2).

However, multivariate analysis revealed only Chinese race; adjusted OR (95% CI); 0.24 (0.07, 0.84) and female gender; 23.7 (5.64, 100.3) were significant prognostic factors for hypovitaminosis D (Table 3).

**DISCUSSION**
The prevalence of healthy adolescents with vitamin D deficiency in Kota Bharu, Kelantan was 16.3% if it is based on the paediatric cut off <30 nmol/L. In MyHeARTs...
Table 2. Univariate analysis for factors affecting vitamin D level

| Variable     | Crude OR (95% CI) | P valuea |
|--------------|-------------------|----------|
| Age          | 0.87 (0.72, 1.06) | 0.191    |
| Gender       |                   |          |
| Male         | 1.00              |          |
| Female       | 22.1 (5.30, 92.3) |          |
| Race         |                   |          |
| Chinese      | 1.00              |          |
| Malay        | 3.79 (1.14, 12.59)| 0.029    |
| Socio-economy|                   |          |
| <RM 2000     | 1.00              |          |
| >RM 2000     | 4.32 (1.12, 16.59)|          |
| BMI          |                   |          |
| Normal       | 1.00              |          |
| Obesity      | 2.74 (1.16, 6.49) | 0.022    |
| Underweight  | 0.61 (0.20, 1.79) | 0.37     |
| L-PTH        | 1.00 (0.99, 1.02) | 0.249    |

*a Simple logistic regression

Table 3. Multivariate analysis for factors associated with vitamin D deficiency

| Variable     | Crude ORb (95% CI) | Adjusted ORb (95% CI) | Wald statistic (df) | P valuec |
|--------------|-------------------|----------------------|---------------------|----------|
| Race         |                   |                      |                     |          |
| Malay        | 1.00              |                      |                     |          |
| Chinese      | 0.26 (0.07, 0.87) | 0.24 (0.07, 0.84)    | 4.99 (1)            | 0.025    |
| Gender       |                   |                      |                     |          |
| Male         | 1.00              |                      |                     |          |
| Female       | 22.1 (5.30, 92.3) | 23.7 (5.64, 100.3)   | 18.6 (1)            | 0.0001   |

*b Multiple logistic regression, the model reasonably fits well. Model assumptions are met. There are no interaction & multicollinearity problems.

| Correlation | p-value | not significant and therefore the model fits |
|-------------|---------|--------------------------------------------|

| Variance Inflation Factor | <10 |
|---------------------------|-----|

| Overall correct classification | 83.8% |
|--------------------------------|-------|

| Area under the curve | 0.762 (95% CI: 0.706, 0.818) |
|----------------------|-----------------------------|

Benefit beyond the recommended levels. Based on inverse relationship between PTH and vitamin D, the level of vitamin D at which PTH is plateauing with increasing level of vitamin D is defined as the cut off for vitamin D deficiency. The effect of high PTH with vitamin D deficiency would result in an increase in bone resorption or skeletal effects but which level of vitamin D that is associated with other non-skeletal effects is still unknown and controversial and this might contribute to different cut-off values of vitamin D used in many other trials.

Based on univariate analysis, significant factors associated with increased odds to have hypovitaminosis D among healthy teenagers were older age, female gender, Malay race, poor socioeconomic status and obesity; OR (95% CI): 0.87 (0.72,1.06), 22.1 (5.30, 92.3), 3.79 (1.14, 12.59), 4.32 (1.12,16.59), 2.74 (1.16, 6.49). From multivariate analysis, there were only two significant predictors for hypovitaminosis D which were female gender and race. We found that female gender had 22.1 times increased odds than male gender to have hypovitaminosis D while Chinese had 74% reduced odds to have hypovitaminosis D compared to Malay. The risk factors associated with hypovitaminosis D are similar to data found in most of the other vitamin D studies. From MyHeA RTS study, the factors that were identified were female gender, obesity, wearing long sleeves, Malay and Indian ethnicity. Female; 5.5 (3.4-7.5), Malay; 3.2 (1.3-8.0), Indians; 4.3 (1.6-12.0) and wearing long sleeves; 2.4 (1.1, 5.4) were the factors associated with increased odds to have hypovitaminosis D after multivariate analysis. A cross sectional study of 402 healthy school children aged 7-12 years old in Kuala Lumpur found that 35.3% of the children had serum 25(OH)D <37.5 nmol/L. The subjects were younger and it was found that the high prevalence was higher in obese boys with chi square=5.958; p=0.016. As expected when a higher value for cut off was chosen, the prevalence would be higher. Compared to other South East Asia countries from SEANUTS survey conducted in 2010/2011 in Indonesia, Malaysia, Thailand and Vietnam, the prevalence of vitamin D deficiency among children with age range 0.5-12 years old were 4.1% in Malaysia, 2% in Thailand, and 11.1% in Vietnam. The subjects were younger than our cohort and the cut off value to define vitamin D deficiency was similar to our definition. Our prevalence is higher most probably since our subjects are older. Older age/adolescents have higher metabolic demands for vitamin D, owing to the rapid growth of the skeleton during puberty and are therefore at higher risk of vitamin D deficiency. Among risk factors associated with vitamin D deficiency from SEANUTS were older age, girls, wearing head scarf or long trousers and darker skin in certain ethnicity especially Indian. In Malaysia (SEANUTS), significant differences were noted between races in which Indians had lower value of vitamin D; 45.6±2.9 compared to Malays; 53.7±1.2, and Chinese; 56.2±1.7 nmol/L. Older age; 1.4 (1.2, 1.5), female gender; 1.8 (1.0, 3.1) had increased odds to have hypovitaminosis D. In Thailand (SEANUTS), older age; 1.1 (1.0,1.2) female gender; 2.2 (1.3,3.7) were associated with increased odds of hypovitaminosis D. In Vietnam (SEANUTS), significant factors that were associated with increased odds for hypovitaminosis D were older age; 1.1 (0.9, 14) and female gender 1.0 (0.6,1.7) and the same were also seen in Indonesia (SEANUTS), with values for older age at 1.1 (1.0, 1.2) and for female gender at 2.7 (1.3, 5.5).
Solar radiation (UVB band of 290-315 nm) stimulates synthesis of pre-vitamin D in the skin from 7-dehydrocholesterol to cholecalciferol, an inactive metabolite of vitamin D. The sun exposure is affected by many factors such as latitude, altitude, season, time of the day, cloud cover, air quality and personal factors which are lifestyle, clothing, time spent outdoor and use of sunscreen. The dose-response of circulating 25(OH)D to cutaneous UVB exposure is dependent on skin pigmentation, age, body composition, genetic factors and baseline 25(OH)D.

Kota Bharu is the capital of Kelantan and it is located at 6.133 N 102.23 E. Abundant sunlight is received throughout the year as Malaysia is located close to the equator. Most of the Malays have darker skin compared to Chinese and this contributed to higher proportion of Malay teenagers with vitamin D deficiency since sunlight is the main source of endogenous vitamin D synthesis. The mean vitamin D (Malay vs Chinese) was 19.0 vs 23.0 ng/mL; (p=0.001). Males have higher level of vitamin D compared to females; 25.4 vs 16.2 ng/mL. Males were significantly taller and heavier compared to females; (162.1 vs 152.8 cm: p=0.006), (56.1 vs 51.1 kg: p<0.001). Majority of the subjects had normal BMI; 292 (80.9%) and the proportion of obesity was only 7.5%. Individuals with obesity are often vitamin D deficient as vitamin D is trapped in adipose tissue potentially because of insufficient lipolytic stimulation and tissue dysfunction/adaptation resulting from adipose expansion. As males were significantly heavier and taller compared to females with normal BMI, this implies higher lean mass than fat mass and therefore higher level of vitamin D compared to female. Other possible associations for a difference in the level of vitamin D between genders are the extent of clothing/head cover and time spent outdoor which were not analysed in this study.

In general, higher rate of obesity and increasing BMI in females are some of the known reasons for lower vitamin D levels in females. Obesity is associated with hypovitaminosis D for some other reasons too. Most of them have less outdoor activity and therefore less sun exposure. There is alteration in the vitamin D feedback mechanism with higher production of 1, 25(OH)2D, that exerts negative feedback control on the hepatic synthesis of serum 25(OH)D. There is also a change in the metabolic clearance due to enhanced uptake by adipose tissue and decreased bioavailability of vitamin D from cutaneous and dietary sources because of its deposition in body fat compartment.

Our study has a few limitations such as limited detailed surveys on diet and other personal/lifestyle factors. The inclusion of dietary survey will be useful since most often the food intake is deficient in vitamin D content. Exploring other lifestyle/personal factors such as time spent in outdoors, clothing, use of sunscreen are some of the important clues that may explain the underlying reasons for vitamin D deficiency. There was some selection bias in terms of number of females compared to males; (227 vs 134) most likely related to convenient sampling and races; Malay vs Chinese; (307 vs 54) since Kelantan has predominantly Malay ethnicity. Initially a total of 367 were recruited but 7 had to be excluded due to missing blood results associated with insufficient blood volume (3) and inadequate number of other races; Indian (2) and Siamese (1).

CONCLUSION
The prevalence of hypovitaminosis D among healthy adolescents in Kota Bharu, Kelantan was 16.9% based on the most recent cut off value of 30 nmol/L. Female gender and Malay race were the significant risk factors associated with hypovitaminosis D. Higher cut off limit used to diagnose vitamin D deficiency would result in overestimation of the prevalence rate.

Statement of Authorship
Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
Both authors declared no conflict of interest.

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