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Journal of Endocrinology, Diabetes & Obesity

Research Article

25-hydroxyvitamin D Level among Vitiligo Patients in Malaysia

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Submitted: 16 December 2017

Accepted: 30 January 2018

Published: 31 January 2018

ISSN: 2333-6692

Keywords
- Vitiligo
- 25-hydroxyvitamin D
- Obesity
- Malaysia
- Sun exposure

Abstract

Introduction: Vitiligo is an acquired depigmenting disorder with significant impact on quality of life. There is a high prevalence of vitamin D deficiency among vitiligo patients worldwide. However, the status of vitamin D among vitiligo patients in Malaysia is unknown.

Objectives: To compare the level of serum 25-hydroxyvitamin D between vitiligo patients and healthy controls, to determine the relationship between vitamin D level and vitiligo severity, and to identify variables affecting vitamin D level.

Method: A single-center, cross-sectional, case-control study assessed anthropometry, serum 25-hydroxyvitamin D level, auto antibodies, sun exposure, and dietary vitamin D intake in patients with vitiligo and in matched controls.

Results: Among 180 subjects, 93 (51.7%) had vitiligo, and 87 (48.3%) were controls. Twice as many vitiligo patients had antithyroperoxidase autoantibody compared to controls, although this was not significant. There was no difference in the mean vitamin D level between both groups. Two-thirds of subjects in both cohorts had vitamin D deficiency or insufficiency. The independent variables affecting vitamin D level were sun exposure index and dietary vitamin D intake, the latter being extremely low in both groups. While vitamin D level was associated with obesity, there was no correlation with Fitzpatrick skin phototype or severity of vitiligo.

Conclusions: Serum vitamin D level is universally low in this study population, with no significant difference between vitiligo and healthy subjects, and this is due to low dietary intake. Since there is no correlation between vitamin D level and severity of vitiligo, vitamin D supplementation may not be justified.

ABBREVIATIONS

DLQI: Dermatology Life Quality Index; NSV: Non-Segmental Vitiligo; VETF: Vitiligo European Task Force; UV: Ultraviolet; BMI: Body Mass Index; BSA: Body Surface Area; SPI: Sun Protection Index; TPO: Thyroperoxidase; RNI: Recommended Nutrient Intake; CLE: Cutaneous Lupus Erythematosus; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index; VDR: Vitamin D Receptor; NMSC: Non-Melanoma Skin Cancer

INTRODUCTION

Vitiligo is an acquired disorder of the skin and mucous membranes that is characterized by well circumscribed, depigmented macules and patches secondary to selective destruction of melanocytes [1,2]. It has a worldwide prevalence affecting up to 2% of the population, almost half of whom present before 20 years of age. There is no difference in the occurrence rate according to skin type or race [1,3]. Vitiligo is a multifactorial polygenic disorder with a complex pathogenesis attributed to autoimmunity, oxidative stress, and/or sympathetic neurogenic disturbance [4]. Many observational studies have shown a significantly higher prevalence of circulating antithyroperoxidase antibodies among vitiligo patients compared to normal individuals [5,6,7], the prevalence ranging from 11-50% [8,9,10]. Vitiligo is disfiguring in all ethnicities and skin types with a major impact on the quality of life of patients. Several studies have shown Dermatology Life Quality Index (DLQI) scores ranging from 4.82-14.72 [11,12].

Vitamin D is a fat-soluble vitamin that humans obtain endogenously when the skin is exposed to ultraviolet (UV) light, and exogenously through dietary intake. Vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng/mL (50 nmol/L). A level of 21-29 ng/mL (52-72 nmol/L) is vitamin D insufficiency, while a level of 30 ng/mL or greater is considered a sufficient level [13,14,15,16]. It has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency [17,18], including Malaysia, despite being a tropical country [17]. This deficiency has been associated with a variety of diseases, including obesity [19] and vitiligo [20,21,22,23].

While there are numerous previous studies addressing the significant relationship between vitamin D level and vitiligo, to the best of the authors' knowledge, there are no similar studies done in Malaysia, hence the rationale of this study.

MATERIALS AND METHODS

This single-center, cross-sectional, hospital-based case-control study was carried out between 1st July 2014 to 31st December 2014 at the Dermatology Clinic of Hospital Tengku Ampuan Rahimah, Klang, Selangor, Malaysia, a tertiary referral center for dermatology cases in the state.

All patients with vitiligo who consented to take part in the study were recruited. Those excluded were those with renal impairment (eGFR less than 60mL/min/1.73m^2) with or without parathyroid disease; osteomalacia, rickets and other metabolic bone; chronic liver disease evidenced by ultrasonic or histopathological evidence of hepatic cirrhosis; dairy allergy; those who have undergone phototherapy within 1 month prior to recruitment; and those who are on medications that may alter vitamin D levels (oral calcium supplements, vitamin D analogues, fish oils or systemic steroids).

Subjects in the control group were selected among patients with non-photosensitive dermatological diseases such as nevi, seborrheic keratosis and verrucae, as well as healthy volunteers among hospital staff. The controls were age-, gender- and race-matched. Similar inclusion and exclusion criteria were applied to this group.

Demographic data, anthropometric measurements and vitiligo assessment (body surface area [BSA] and DLQI scoring) were carried out. The total vitamin D intake (mcg/day) was determined by multiplying the vitamin D content of individual foods with portion size, while the sun exposure/protection index (SPI) was calculated as the number of hours of sun exposure per week multiplied by the fraction of BSA exposed to sunlight [24,25].

Venous blood was assayed for serum calcium, phosphate, thyroxine (T4), thyroid stimulating hormone, anti-thyroglobulin and anti-thyroperoxidase antibodies, anti-nuclear antibodies, and serum 25-hydroxyvitamin. The level of serum vitamin D was classified according to deficiency, insufficiency or sufficiency based on the recommended classification by Holick [26].

All data analysis was carried out using SPSS (IBM Corp. Released 2011 IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) Descriptive analysis was carried out for demographic data. Analytical statistics was used to determine the association of serum vitamin D level with other variables. Multivariate regression analysis was performed to determine those variables that independently affected serum vitamin D levels.

Ethical approval was obtained from the Ministry of Health of Malaysia Medical Research Ethics Committee (National Medical Research Registry identification number: NMRR-14-1270-20502).

RESULTS AND DISCUSSION

A total of 180 patients were enrolled in the study, out of which 93 (51.7%) suffered from vitiligo, while 87 (48.3%) were healthy controls (Table 1). There was an equal number of male and female individuals suffering from vitiligo in this study population. Although worldwide, large-scale epidemiological studies have demonstrated a slight female preponderance of the disease, this discrepancy has been found to be statistically not significant and attributed to an increased reporting of cosmetic concerns by female patients. Indian ethnicity made up half of the patients in both groups, followed by Malay and Chinese. This ratio is similar to the outpatient attendance at the clinic. Almost all subjects had either Fitzpatrick skin phototype III (52.8%) or IV (46.1%) (Table 1) reflecting the fact that Indian and Malay patients who generally have darker skin, make up close to 90% of the study population. Three-quarters of subjects in both cohorts are either overweight or in the obese class I category. There was no statistically significant difference in mean body weight, body mass index (BMI), and abdominal girth between the vitiligo and control groups (Table 2).

Among patients with vitiligo, 86 (92.5%) had non-segmental type of the disease, while 7 (7.5%) had segmental disease. From literature, it is noted that there is a stronger association between non-segmental vitiligo (NSV) and autoimmunity and/or inflammation, as well as a higher likelihood of positive family history of vitiligo and/or autoimmune disease [27]. This should prompt healthcare providers to be more vigilant when screening patients with NSV for autoimmune disorders. The median duration of disease was 3.0 years, with an interquartile range (IQR) of 8.0 years (range: 2 months to 30 years). The median BSA involvement was 2.0% (interquartile range [IQR]=7.3; range: 1-90%), and the median DLQI score was 4.2 (IQR=3.31; range: 0-12). Nine vitiligo patients (9.7%) had a DLQI score above 10, which indicates significant impairment in quality of life. As such, dermatologists and general physicians should be more vigilant in picking up subtle warning signs and symptoms of depression, anxiety and suicidal ideation.

There was no statistically significant difference in mean serum thyroxine level between the vitiligo and control groups (15.62±2.36 pmol/L and 15.65±2.26 pmol/L, respectively; *p=0.930*). There was also no statistically significant difference in mean serum thyroid stimulating hormone (TSH) level between both groups (2.16±2.04 mIU/L and 2.01±2.00 mIU/L, respectively; *p=0.628*). However, there were three times as many vitiligo patients with antithyroperoxidase and/or antithyroglobulin autoantibodies compared to controls (22 [23.6%] and 8 [9.2%], respectively; *p=0.009*), echoing numerous other reports on the strong association between vitiligo and autoimmune thyroid disease. As the onset of vitiligo can predate overt autoimmune thyroid dysfunction by many years, it may be essential to screen patients with vitiligo for thyroid autoantibodies. Both the Hamburg Study and Uncu et al., recommend an annual screening frequency for both children and adults with vitiligo [28,29].

This study found the serum vitamin D level to be low in both cohorts and there was no significant difference in the mean serum vitamin D level between the vitiligo and control groups (25.32±9.92 ng/mL and 24.59±11.71 ng/mL, respectively; *p=0.652*. 37 (39.8%) patients with vitiligo and 42 (48.3%) controls were found to be deficient in vitamin D, 29 (31.2%) patients with vitiligo and 23 (26.4%) controls had insufficient levels while 27 (29.0%) patients with vitiligo and 22 (25.3%) of controls had sufficient levels of vitamin D. Nevertheless, there was no significant difference between vitamin D deficiency,

Table 1: Age, Gender, Ethnicity and Fitzpatrick Skin Phototype of the Study Population.

VARIABLE	VITILIGO (N=93) Mean ± SD / N (%)	CONTROL (N=87) Mean ± SD / N (%)	*P*
Age (years)	40.43 ± 19.21	39.95 ± 18.60	*0.860*
Gender			
Male	46 (49.5)	43 (49.4)	*0.885*
Female	47 (50.5)	44 (50.6)	
Ethnicity			
Malay	33 (35.5)	33 (37.9)	
Chinese	11 (11.8)	11 (12.6)	*0.838*
Indian	49 (52.7)	43 (49.4)	
Fitzpatrick Skin Phototype			
II	1 (1.1)	1 (1.1)	
III	49 (52.7)	46 (52.9)	*0.808*
IV	43 (46.2)	40 (46.0)	

SD: standard deviation

Table 2: Weight, Body Mass Index and Abdominal Girth of the Study Population.

VARIABLE	VITILIGO (N=93) Mean ± SD / N (%)	CONTROL (N=87) Mean ± SD / N (%)	*P*
Weight (kg)	63.88 ± 13.71	62.61 ± 12.32	*0.500*
Body Mass Index	22.65 ± 4.08	22.06 ± 3.78	*0.296*
BMI (kg/m^2)			
Underweight/Normal (<18.5 – 24.9)	23 (24.7)	15 (17.2)	
Overweight/Obese Class I (25.0 – 34.9)	70 (75.3)	72 (82.8)	*0.226*
Abdominal Girth (cm)	81.12 ± 11.76	79.65 ± 11.03	*0.370*

BMI: body mass index; SD: standard deviation

Table 3: Comparison between Dietary Vitamin D Intake among Various Populations.

Author, year	Country	n	Median daily dietary vitamin D intake (mcg)	Proportion of subjects with inadequate (<15mcg/day) dietary vitamin D intake (%)
Musa, 2004	Malaysia	276	8.75	100
Puri, 2008	India	404	2.20	86.7
Lee, 2011	Malaysia	177	2.85	88.0
Musa, 2013	Malaysia	400	4.92	92.5
This study, 2016	Malaysia	93	2.04	77.8

Table 4: Comparison between Studies of Serum Vitamin D level in Vitiligo Patients.

Author, year	Country	n	Number of healthy control	Serum Vitamin D	Factors associated with low serum Vitamin D					
					Gender	Higher skin phototype	Higher BSA involvement	Higher BMI class	Presence of other autoimmune diseases	Others
Silverberg et al, 2010	USA	45	-	2/3 low	No	Yes	No	NS	Yes	Low dietary intake
Xu et al, 2012	China	201	70	Low in both	Female	NS	NS	NS	Yes	
Beheshti et al, 2014	Iran	100	-	Low	No	No	NS	NS	No	Outdoor job
Khurrum et al, 2016	Saudi Arabia	150	150	Low in both	Male	NS	NS	NS	NS	Younger age Family history
This study, 2016	Malaysia	93	87	**Low in both**	No	No	No	**Yes**	No	Low dietary intake

NS: not studied

Table 5: Serum Vitamin D Level and Obesity Class.

	Underweight (N=43) Mean ± SD / N (%)	Normal (N=99) Mean ± SD / N (%)	Overweight (N=23) Mean ± SD / N (%)	Obese I (N=15) Mean ± SD / N (%)	*P*
Serum Vitamin D (ng/mL)	18.91 ± 5.06	25.93 ± 10.44	26.91 ± 14.24	20.51 ± 8.81	*0.011*
Vitamin D Sufficiency (≥ 30 ng/mL)	5 (11.6)	32 (32.3)	8 (34.8)	4 (26.7)	
Vitamin D Insufficiency (21 – 29 ng/mL)	16 (37.2)	28 (28.3)	6 (26.1)	2 (13.3)	
Vitamin D Deficiency (≤ 20 ng/mL)	22 (51.2)	39 (39.4)	9 (39.1)	9 (60.0)	*0.005*

SD: standard deviation

vitamin D insufficiency and vitamin D sufficiency and both study groups (*p=0.257*, *p=0.489*, *p=0.579*, respectively).

Multivariate regression analysis identified the two independent variables affecting serum vitamin D level as dietary vitamin D intake (Spearman correlation = 0.150; *p=0.045*) as well as the sun protection index (SPI) (Spearman correlation = 0.295; *p< 0.001).*

The median daily dietary vitamin D intake for both vitiligo and control groups is way below the daily recommended intake of 15 mcg, as proposed by Institute of Medicine, Food and Nutrition Board of America [30]. The median daily dietary vitamin D intake for the vitiligo group was 1.72 mcg (IQR=3.39), and 2.35 mcg (IQR=4.89) for the control group (*p=0.228*). Based on the cut-off value of 15 mcg, 140 subjects (77.8%) were having inadequate dietary intake, while only 40 subjects (22.2%) were having adequate intake. While there was no difference in dietary vitamin D intake between both genders (*p=0.720*), there were significant differences noted among the various ethnicities, with more Indians having inadequate intake compared to the other ethnicities (*p=0.0001*), while more Malays have adequate intake compared to the other ethnicities (*p=0.0001*). There was no difference among Chinese subjects (*p=0.112*).The low dietary vitamin D intake among subjects in both our cohorts is not something new or peculiar. Two other local studies found only 7.5% [24] and 12% [31] of urban dwellers meeting the recommended nutrient intake (RNI) (National Coordinating Committee on Food and Nutrition, Ministry of Health Malaysia. 2005). Both these studies, however, found no correlation between serum vitamin D level and dietary vitamin D intake, similar to the observation by Puri's group [32] (Table 3). Our study, on the other hand, found dietary intake of vitamin D to be an independent variable affecting serum vitamin D concentration. This discrepancy may be due to the fact that there is a wide variety of Malaysian foods without a complete pre-determined nutrient content, as well as varying study methodologies employed by the studies, including differences in food diary and 24-hour diet recall bias. Thus, the estimation of vitamin D content in food based on product label information and individual food portion, may potentially lead to less accurate levels, hence the difference in observations.

The median sun protection index (SPI) of the vitiligo group was 1.47 (IQR=2.66), while the median SPI of the control group was also 1.47 (IQR=2.45). Expectedly, this difference was not statistically significant (*p=0.887*).

Other studies have also identified similar as well as additional variables affecting serum vitamin D levels in vitiligo, such as female gender [21], male gender [22], outdoor job [33], younger age [22], family history [22], higher skin phototype [20], presence of other autoimmune disease [20,21], in addition to low dietary intake [20] (Table 4).

This study also showed that vitamin D level is associated with obesity. Among the 70 vitiligo subjects who were either of normal weight or who were underweight, 18 (25.7%), 24 (34.3%) and 28 (40.0%) were sufficient, insufficient and deficient respectively, while among the 23 vitiligo subjects who were either overweight or who were in the obese class I, 9 (39.1%), 5 (21.7%) and 9 (39.1%) were sufficient, insufficient and deficient respectively. Among the 72 control subjects who were either of normal weight or who were underweight, 19 (26.4%), 20 (27.8%) and 33 (45.8%) were sufficient, insufficient and deficient respectively, while among the 15 control subjects who were either overweight or who were in the obese class I, 3 (20.0%), 3 (20.0%) and 9 (60.0%) were sufficient, insufficient and deficient respectively. Fischer's exact test showed that the differences in vitamin D status among the obesity classes was statistically significant (*p=0.005*).There was a positive correlation between serum vitamin D level and the various classes of obesity (*p=0.011*) (Table 5). This finding is in keeping with the current, accepted understanding that vitamin D deficiency is strongly linked with increasing obesity [19,34,35,36]. This is postulated to be due to the sequestering of vitamin D, a fat-soluble vitamin, by body fat. In a recent meta-analysis by Pereira-Santos' group involving 23 articles, it was found that vitamin D deficiency was more prevalent in obese subjects, irrespective of age, latitude, and cut-offs to define vitamin D deficiency [37].

It was also found that there was no significant association between level of serum vitamin D and percentage of BSA involved (Spearman correlation = 0.194; *p=0.062*). There was also no significant association between level of serum vitamin D with DLQI score (Spearman correlation = 0.016; *p=0.878*). Not surprisingly, a higher BSA involvement correlated positively with a higher DLQI score (Spearman correlation = 0.496; *p< 0.001*). While BSA involvement and the DLQI score were traditionally used as indicators of severity of vitiligo, no correlation was found between the level of serum vitamin D and the BSA involvement, similar to a number of previous studies [20,38,39].

CONCLUSION

Serum vitamin D concentration is universally low in our study population, and there is no significant difference in the vitamin D level between subjects with vitiligo and healthy controls. There is also no correlation between the level of vitamin D and the severity of vitiligo. This low serum vitamin D level is due to low dietary vitamin D intake, sun exposure and obesity.

ACKNOWLEDGEMENTS

We, the authors, thank the Director-General of Health, Malaysia, for his permission to publish this article. We would also like to thank the Clinical Research Center of Malaysia, the Science Laboratories of University Malaya Medical Center, Kuala Lumpur, and the staff of the Department of Dermatology, Hospital Tengku Ampuan Rahimah, Klang, for their assistance in conducting this study.

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Cite this article

RamalingamR, Tang MM (2018) 25-hydroxyvitamin D Level among Vitiligo Patients in Malaysia. J Endocrinol Diabetes Obes 6(1): 1112.