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Serum vitamin D in Indian children with vernal keratoconjunctivitis

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Abstract

● AIM: To determine the vitamin D levels in vernal keratoconjunctivitis (VKC) patients in Indian population.

● METHODS: A total of 30 non-atopic healthy children and 30 children having VKC were included in the study. The serum vitamin D levels and the time spent outside was compared between the two groups ($P<0.05$).

● RESULTS: The mean serum vitamin D level in the VKC group was significantly lower (mean 19.17±10.76 ng/mL) compared to the control group (mean 31.19±9.09 ng/mL) ($P=0.0003$). The vitamin D levels were found to be deficient (10-20 ng/mL) in 43.33%, whereas severe deficiency
(<10 ng/mL) was found in 20% of the VKC patients. The deficiency of vitamin D correlated with the level of severity of VKC ($P<0.02$). The time spent outside in the VKC group was 1.07±0.76h, whereas in the healthy subjects it was 2.08±0.72h ($P<0.0001$), and it showed a significant correlation with the serum 25 (OH) D3 levels ($r=0.478$, $P<0.001$).

● CONCLUSION: The study shows that children with VKC had a significantly lower serum vitamin D levels as compared to the healthy children which correlated with time spent outside. The severity of VKC also correlated with the severity of vitamin D deficiency which suggests that vitamin D plays an important role in maintaining ocular surface health.

● KEYWORDS: vernal keratoconjunctivitis; vitamin D deficiency; children

INTRODUCTION

Vernal Keratoconjunctivitis (VKC) is a chronic, sight threatening, allergic disease of the eye, affecting mainly young males. It is characterized by a seasonally recurring, bilateral inflammation of the conjunctiva and the cornea. Vitamin D deficiency has been implicated in the pathophysiology of VKC along with endocrine, neurogenic, genetic, environmental and socioeconomic risk factors.

There are 4 types of allergic conjunctivitis which have different types of pathological reactions: simple allergic conjunctivitis (seasonal, acute and perennial) is type I hypersensitivity reaction. Atopic and giant papillary conjunctivitis is combined type I and IV hypersensitivity reaction. Vernal Keratoconjunctivitis resembles Type I (Ig E dependent) and IV (Ig E independent) hypersensitivity reaction. It shows the presence of eosinophils, mast cells, fibroblasts, T and B cells which plays an active role in its pathogenesis.

VKC commonly affects young boys, but both sexes can be involved. Onset is usually around 5 years of age, around 95% of the cases show regression during or

soon after puberty. Though the usual presentation is during spring and summer seasons, perennial cases are also seen. Symptoms consist of intense itching, blurred vision, lacrimation, photophobia, blepharospasm and mucoid discharge. The disease may be classified as tarsal (primarily involving the upper tarsal conjunctiva), limbal, or mixed phenotype. Tarsal disease presents with conjunctival hyperaemia and flat-topped macro-papillae (<1 mm) known as cobblestone papillae, or giant papillae (>1 mm) on the superior tarsal conjunctiva, whereas the limbal disease presents with gelatinous aggregates of epithelial cells and eosinophils (Horner-Trantas dots) at the limbus; corneal involvement may result in punctate epithelial keratitis, epithelial macro-erosions, shield ulcer and plaque formation.

Vitamin D is an important fat-soluble prohormone, having numerous functions in the body, including the regulation of calcium and phosphate meatabolism. The effects are mediated via a receptor called as VDR. VDR has also been discovered in tissues and cells which are not involved in calcium homeostasis, such as on T cells, B cells, neutrophils, macrophages, and dendritic cells. It has been shown to have a role in the regulation of immunity, cells proliferation and differentiation, angiogenesis and apoptosis. Vitamin D has been shown to suppress the allergic pathways by inhibiting the dendritic cells maturation, migration and reprogramming as tolerogenic phenotype, decreasing the interleukin-12 (IL-12), IL-23 and cytokine production, inducing IL-10 secreting regulatory T cells, and inhibiting Th1 and Th17 cells.

Other effects such as prevention of cardiovascular, immunerelated and infectious diseases have also been proposed and many studies have suggested a correlation between vitamin D levels and immuno-mediated and atopic diseases.

Although many researchers evaluated the relationship between vitamin D and allergic disease providing conflicting results, its levels in patients with VKC have been assessed in only two studies: Zicari et al conducted a randomised prospective study on 110 children in Italy demonstrated that children affected by VKC have lower vitamin D levels when compared to healthy controls and highlights a significant correlation between its levels and disease severity.

Another study conducted in Turkey by Bozkurt et al on 62 non-atopic healthy children and 29 VKC children showed that children with VKC in the studied population had lower serum vitamin D levels compared with age and sex matched healthy children and half of these patients had severe vitamin D deficiency, which seems to develop secondary to decreased sun exposure.

A recent study in Italy published in 2019 with 242 children with active VKC showed that ocular treatment with immunomodulator eye drops (cyclosporine or tacrolimus) could allow for improvement in serum vitamin D levels. Few other studies have mentioned vitamin D deficiency as risk for developing seasonal allergic conjunctivitis, childhood asthma and systemic allergies.

In India, no such study has been done so far which correlates the association between VKC and serum vitamin D levels. The present study is intended to investigate the serum vitamin D levels in children affected by vernal keratoconjunctivitis.

SUBJECTS AND METHODS

Ethical Approval The study was approved by the Ethical Committee (Institute Ethics Committee, V.M.M.C. and Safdarjung hospital, New Delhi, India, 110029) and informed consent was taken from the parents.

A total of 30 VKC children and 30 healthy children were included in this case control study from April 2108 to November 2018. Newly diagnosed VKC patients with a VKC score ⩾7, in the age group of 5-15 years, willing to follow up were included in the study. Individuals having any prior ocular surgery, history of asthma or systemic allergy, any other ocular disease except refractive errors, history of rheumatoid arthritis, cystic fibrosis, sarcoidosis, thyroid dysfunction, obesity and on any drugs like barbiturates, bisphosphonate, sulphasalazine, omega 3 fatty acids, calcium, and vitamin D, were excluded from the study. Control subjects were chosen from healthy
children with no history of atopy or any ocular diseases other than refractive errors.

A meticulous history taking was done to rule out the exclusion criteria. Patients were asked about the symptoms like itching, photophobia, tearing, foreign body and burning sensation. Patients were also asked about how many hours they spend outdoors on an average per day. Clinical examination was done by evaluation of anterior segment using slit lamp examination to look for conjunctival hyperaemia, tarsal and/or limbal papillae, giant papillae, punctate epitheliopathy, or shield ulcer in patients with VKC. Best corrected visual acuity determination,
refraction, fundus examination, corneal topography was also done for all the patients.

Determination of VKC score: 1) Conjunctival hyperaemia; 2) Tarsal and/or limbal papillae; 3) Giant papillae; 4) Itching; 5) Photophobia; 6) Tearing; 7) Foreign body sensation; 8) Burning sensation. Each variable was graded as follows: 0: absent, 1: mild, 2: moderate, 3: severe.

In the score other two parameters were included: Duration of symptoms (0 if <1 years; 1 if >1 years and 2 if >2 years); Corneal involvement (0: absent, 1: de-epithelialization, 2: keratitis, 3; ulcer). Children with a total score ⩾ 7 were included in the study.

After the diagnosis, patients were divided into four grades of VKC according to presenting symptoms and signs, i.e. mild, moderate, severe and blinding.

Fasting venous blood samples from the antecubital vein was obtained in the morning after overnight fasting and put into EDTA anticoagulated tubes. Serum vitamin D level was analysed by chemiluminescence assay in the department of pathology.

In this study serum 25 (OH) D3 levels were measured, as it has a significantly more stable hormone-receptor complex than 25 (OH) D2, and has been shown to provide levels of vitamin D in circulation more effectively. Detection limit for 25(OH) D3 is 5 ng/mL. The Endocrine Society Clinical Practice Guidelines suggested considering deficiency if 25 (OH) D is below 20 ng/mL (50 nmol/L), while levels <10 ng/mL are accepted as severe vitamin D deficiency[29-30]. The children having vitamin D deficiency were referred to the department of paediatrics for treatment and vitamin D supplementation.

Statistical Analysis Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non-parametric test was used.

Statistical tests were applied as follows: Quantitative variables were compared using Independent T test/Mann-Whitney Test(when the data sets were not normally distributed) between the two groups and ANOVA test for correlation of vitamin D level with severity. Qualitative variables were correlated using Chi-Square test.

Pearson correlation coefficient was used to assess the association of severity of VKC with vitamin D deficiency severity. A P value of <0.05 was considered statistically significant.

RESULTS

There were 30 patients in the VKC group (25 males, 83.33%; 5 females, 16.67%) and 30 patients in the control group (21 males, 70%; 9 females, 30%), with no statistical differences (P=0.22).

The mean ages of the VKC group was 8.27±2.79 years and the control group was 8.9±2.52 years, with no statistical difference (P=0.922).

The best corrected visual acuity (BCVA) ranged from 6/6-6/24, with 53.33% having 6/6, 40% having 6/9, 3.33% having 6/12 and 3.33% having 6/24 in VKC group. All the controls had a BCVA of 6/6.

The mean spherical refraction in the VKC group was -0.69±1.01, and in the control group was -0.68±1.02. The mean maximum (K1) and minimum (K2) topographic keratometric values in the VKC group were 43.83±0.78 D and 43.42±0.79 D respectively, and in the control group were 43.9±0.82 D (K1) and 43.57±0.87 D (K2). VKC was tarsal in 13 subjects (43.33%), limbal in 3 subjects (10%) and mixed in 14 subjects (46.67%). The severity of VKC was mild in 1 (3.33%),
moderate in 19 (63.33%), severe in 9 (30.0%) and blinding in 1 (3.33%) patient.

The mean serum 25 (OH) D3 level in the VKC group was significantly lower (mean 19.17±10.76 ng/mL, median 17.05 ng/mL, range 5-53.4 ng/mL) as compared to the control group (mean 31.19± 9.09 ng/mL, median 32.15 ng/mL, range 12-49.2 ng/mL) (P=0.0003).

The vitamin D levels were found to be sufficient (>30 ng/mL) in 13.33%, in-sufficient (21-29 ng/mL) in 23.33%, deficient (10-20 ng/mL) in 43.33% and severe deficiency (<10 ng/mL) was found in 20% of the VKC patients. In the control group, the vitamin D levels were sufficient (>30 ng/mL) in 60%, insufficient (21-29 ng/mL) in 26.67%, deficient (10-20 ng/mL) in 10% and severe deficiency (<10 ng/mL) was found in 3.33% of controls.

According to severity of the disease, the mean vitamin D level in mild VKC was 30 ng/mL, moderate: 21.06±11.61 ng/mL, severe: 13.92±7.87 ng/mL and in blinding: 19.5 ng/mL (P=0.157). The correlation of deficiency of vitamin D with the increased levels of severity of VKC was statistically significant (P<0.02).

The VKC score and the serum vitamin D levels did not show a statistically

significant correlation (correlation coefficient -0.342, P=0.0646) but was clinically significant.

The time spent outside in the VKC group was 1.07±0.76h, with a median of 1h and range 0-3h, whereas in the healthy subjects it was 2.08±0.72h, median 2h and range 1-4h, which was statistically significant (P<0.0001).

The time spent outside correlated with the vitamin D levels, with higher Vitamin D levels in children who spent more time outside (r=0.478, P<0.001).

DISCUSSION

Vernal keratoconjunctivitis is one of the disorders in the vast spectrum of allergic eye diseases. Various studies have been done evaluating the risk factors for seasonal allergic conjunctivitis. It has been suggested that Vitamin D deficiency may play a role in the onset of allergic diseases. In this study, a total of 60 subjects were taken, 30 in the VKC group and 30 in the control group (non-VKC group). There was no statistical difference in the age and sex distribution between the two groups.

Of the 30 patients, majority had mixed VKC (46.47%), followed by tarsal (43.33%) and limbal (10%). 19 patients (63.3%) had a moderate (intermittent) disease and 9 (30%) had a severe disease. One patient had a mild disease and one had blinding disease. The child with mild disease was included in the study due to the severity of his presenting symptoms, which resulted in his severity score being 7. We encountered 2 patients with chronic moderate VKC but as they were already on topical medications, they were not included in the study. The mean VKC score was 10.33±2.62 .

Tear film measurements in four different ethnic groups: Malay, Chinese, Indian and Nigerian

Madhavendra Bhandari, Boo Sheau Yun

Abstract

● **AIM**: To compare the non-invasive tear film break-up time (NIBUT), tear break up time (TBUT), basal tear secretion (BTS) and blink rate in four ethnic groups: Malay, Chinese, Indian and Nigerian.

● **METHODS**: Totally 120 healthy (61 males and 59 females) subjects (without dry eye symptoms and ocular surface disorder) with the age 20 to 39 years were recruited; 30 were Malays, 30 were Chinese, 31 were Indians and 29 were Nigerians. Based on McMonnies questionnaire and clinical examination, normal subjects were selected. NIBUT, TBUT, BTS were assessed in only one eye (right) of each subject and blink rate was also assessed.

● **RESULTS**: There was significant difference in the NIBUT, TBUT, BTS and blink rate among 4 different ethnic groups (P=0.018, 0.001, 0.011, and 0.004 respectively). No statistically significant difference of NIBUT, TBUT, BTS and blink rate was found between the genders among different ethnic groups. Indian had higher median for NIBUT (10±6s), TBUT (7±5s) and BTS (20±20 mm) than other races. Chinese had lower median for NIBUT (7.5±4s) and TBUT (4±2s) while Malay had for BTS (9.5±16 mm) among the groups. There was no significant correlation of blink rate with NIBUT (r=-0.119, P=0.195), TBUT (r=-0.086, P=0.352), and BTS (r=-0.123, P=0.180) respectively.

● **CONCLUSION**: The tear-film measurement values are variability in four ethnic groups.

● **KEYWORDS**: non-invasive tear film break-up time; tear break up time; basic tear secretion; blink rate; ethnicity

Citation: Bhandari M, Sheau YB. Tear film measurements in four different ethnic groups: Malay, Chinese, Indian and Nigerian. Int Eye Res 2021;69-73

INTRODUCTION

Measurements of the stability and volume of tear film are important while assessing the ocular surface in cases of dry eye syndrome. Dry eye syndrome and tear film dysfunction are synonymous. Tear film dysfunction leads to ocular complications such as excessive tearing, conjunctival and corneal surface damage, and vision changes. Therefore, the tear stability and volume is essential in assessing contact lens fitting, cataract and refractive surgery, and also to know the outcome of dry eye treatment. The normal values of tear stability and volume may differ in different ethnic groups. Differences in eyelid anatomy (e.g. palpebral aperture size and lid

margin apposition against the ocular surface) between Asians and non-Asians may contribute to variability in tear film thickness and tear-film stability[10]. Studies suggesting wider palpebral aperture sizes and palpebral aperture width lead to more exposure and greater disruption in tear film.

There are separate reports on tear stability and tear volume in different ethnic groups living in different environments. However, due to the difference in instrument designs and observational procedures; there are differences in tear film measurements. The purpose of this study was to determine the tear stability and tear volume in Chinese, Malay, Indian and Nigerian ethnic groups living in the same climate.

SUBJECTS AND METHODS

Ethical Approval The study was carried out in the Optometry Clinic at Twintech International University College of Technology, Faculty of Optometry, Kuala Lumpur, Malaysia. Informed consent was obtained from all participants prior to any measurement. The study was conducted according to the tenets of Declaration of Helsinki.

This was a prospective cross sectional study. A total of 120 subjects (age range 20-39 years) were recruited. The subjects were from 4 different ethnicities; 30 Malays, 30 Chinese, 31 Indians and 29 Nigerians. All the subjects were students, 3 ethnics groups; Malays, Chinese, and Indians were Malaysian whereas, Nigerians were from Nigeria, studying in Malaysia under same university.

The inclusion criteria set for this study was as follow: age between 20 to 39 years, currently not on any medication, not contact lens wearers, have no history of any ocular surgery, have habitual visual acuity of 20/30 or better, have normal appearance of all corneal layers on slit lamp examination and with no corneal lesions. Individuals with autoimmune disorders, and females during pregnancy, menstruation, lactation, and hormone replacement therapy were excluded. Subjects having a history of dry eye and Mc-Monnies questionnaire score more than 14.5 were also excluded from this study to rule out dry eye.

Habitual visual acuity was measured using a Snellen chart. Tear film status was then evaluated. Blink rate was measured first. The number of blinks made per minute was recorded. Non-invasive tear film break-up time (NIBUT), tear break up time (TBUT), basic tear secretion (BTS) were assessed in only one eye (right) of each subject.

The NIBUT test, which measures tear stability without the introduction of a foreign substance into the tear film, was assessed next by using a Shin-Nippon S0-21 keratometer. The subject was seated carefully and the keratometer well adjusted for the right eye with the mires in focus. The subject was asked to blink once and then refrain from blinking. A stopwatch was started after the last complete blink. At the first sign of any distortion of the mires, the stopwatch was stopped and the time noted. If the subject blinked between measurements, the test was repeated after several blinks. The time interval between the last blink and the first sign of mire distortion was recorded in seconds as the NIBUT. The test was repeated three times to increases the reliability and the average was then taken.

TBUT is the time needed for the appearance of dark spots of the tear film after blinking of the fluorescein treated eye. For the measurement of TBUT, the upper eyelid of the right eye was slightly lifted, and the fluorescein strip was then used to stain the tear film. The subject was asked to blink a few times for homogenous mixing of fluorescein in tear film. Then, the tear film was observed under cobalt-blue filter. The stopwatch was started after the last blink and the appearance of dry spots on the corneal surface was detected and recorded in seconds. An average of three readings was taken.

After resting for 10min, BTS was measured using Schirmers strips (Whatman no 41 filter paper, tear touch). A drop of tropical anaesthesia (0.5%, Alcaine) was instilled in the tested eye. After 2min, the Schirmers strip was placed at the lateral one third of the lower eyelid of the eye. The subject was asked to blink normally. After 5min, the strip was removed. The length of the wetted strip from the fold was measured.

All the subjects were tested between 10 a.m.-12 p.m., at least after 2h of waking. Tear film measurements were performed in the same room to maintain a relatively constant temperature and humidity. Slit lamp biomicroscopy of the anterior segment (lids, cornea, and conjunctiva) was also performed. Meibomian gland dysfunction was recorded according to Efron grading scale. The grade 0-1 was considered as normal in this study.

Statistical Analysis Statistical analyses were done by using SPSS version 16.0 statistical software and MS Excel 2007. Test of normality was performed by Kolmogorov-Smirnov test. The measurement variables were not normally distributed. Kruskal-Wallis test was performed among four different ethnic groups. Mann-Whitney test was performed between the ethnic groups and sex groups. To evaluate correlation between variables, Spearman correlation coefficient was used. A $P \leqslant 0.05$ was set for statistical significance.

RESULTS

A total of 120 subjects (mean: 23.07±2.69y; range 20-39y) were examined. There were 61 (50.8%) male and 59 (49.2%) female subjects. Thirty (25%) subjects were Malays, 30 (25%) were Chinese, 31 (25.8%) were Indians and 29 (24.2%) were Nigerians. There was no statistically significant difference in age among ethnic groups. There was statistically significant difference in the NIBUT (P=0.018), TBUT (P=0.001), BTS (P=0.011) and blink rate (P=0.004) among ethnic groups.

Indians had the highest NIBUT, TBUT, and BTS whereas Chinese had the lowest mean NIBUT and TBUT. The NIBUT, TBUT and BTS amongst Indians were significantly higher compared to Malays, and Chinese. The blink rate for Malays was significantly higher than for Indians, Chinese and Nigerians.