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Blood Levels of Vitamin D in Teens and Young Adults with Myopia

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Abstract

Purpose—Longitudinal data suggest that time outdoors may be protective against myopia onset. We evaluated the hypothesis that time outdoors might create differences in circulating levels of vitamin D between myopes and non-myopes.

Methods—Subjects provided 200μl of peripheral blood in addition to survey information about dietary intakes and time spent in indoor or outdoor activity. The 22 subjects ranged in age from 13 to 25 years. Myopes (n = 14) were defined as having at least −0.75D of myopia in each principal meridian and non-myopes (n = 8) had +0.25D or more hyperopia in each principal meridian. Blood level of vitamin D was measured using liquid chromatography/mass spectroscopy.

Results—Unadjusted blood levels of vitamin D were not significantly different between myopes (13.95 ± 3.75ng/ml) and non myopes (16.02 ± 5.11ng/ml, p = 0.29), nor were the hours spent outdoors (myopes = 12.9 ± 7.8 hours; non-myopes = 13.6 ± 5.8 hours; p = 0.83). In a multiple regression model, total sugar and folate from food were negatively associated with blood vitamin D, while theobromine and calcium were positively associated with blood vitamin D. Myopes had lower levels of blood vitamin D by an average of 3.4ng/ml compared to non-myopes when adjusted for age and dietary intakes (p = 0.005 for refractive error group, model R^2 = 0.76). Gender, time outdoors, and dietary intake of vitamin D were not significant in this model.

Conclusions—The hypothesis that time outdoors might create differences in vitamin D could not be evaluated fully because time outdoors was not significantly related to myopia in this small sample. However, adjusted for differences in the intake of dietary variables, myopes appear to have lower average blood levels of vitamin D than non-myopes. While consistent with the hypothesis above, replication in a larger sample is needed.

Keywords

vitamin D; myopia; refractive error

Debates about the causes of myopia have always been classic nature vs. nurture discussions fueled by ample evidence for each side. On the side of nature, myopic parents tend to have myopic children more often than non-myopic parents,[1–2] heritabilities are high, on the order of 0.8 to nearly 1.0,[3–4] and recent molecular studies have identified numerous genetic loci associated or linked with myopia.[5–6] On the side of nurture, excessive near work has been a putative risk factor for myopia for at least 400 years. There is evidence in support of the

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stereotype; myopic children spend more time in reading and other close work than non-myopic children.[7–10] However, recent large, longitudinal studies have shown that the amount of reading or other close work does not increase the risk of ***becoming*** myopic.[2, 11] The additional close work that myopic children engage in did not precede, and therefore likely did not cause, their myopia.

Time spent outdoors has recently become a variable of interest in myopia research. Like near work, many cross-sectional studies find an association between myopia and time outdoors; myopic children spend less time outdoors than non-myopic children.[10, 12–14] A recent study indicates that there may be seasonal variation in this effect with smaller differences between refractive error groups in the summer compared to during the school year.[15] Unlike near work, this cross-sectional association has been borne out in a longitudinal study, suggesting that more time outdoors might actually be protective and reduce the risk of the onset of myopia.[2] The magnitude of this effect may be substantial. For example, the probability of developing myopia by the eighth grade for a third grade child who has two myopic parents and engaged in 0–5 hours per week of sports/outdoor activity was estimated at about 0.60. This probability was reduced to about 0.20 if the third grade child with two myopic parents engaged in over 14 hours per week of sports/outdoor activity.[2] Physical activity by itself, whether indoors or outdoors, does not carry the same protective effect of simply spending time outdoors.[13–14] Therefore the relevant protective factor appears to be merely being outside rather than some specific activity such as exercise. One might argue that the effects of time outdoors are just the effects of near work in reverse, that time spent outdoors is just time spent not reading. Numerous studies have investigated this question and none has found evidence of this tradeoff behavior; children's time outdoors is not negatively correlated with reading or other close work. Correlations are either not significant or slightly positive, with children spending more time reading and outdoors.[2, 13–14]

Several theories have been proposed as the physiological basis of a protective effect on myopia of time spent outdoors. Among these has been a better quality retinal image during distance fixation outdoors.[2, 13] Ocular growth is sensitive to retinal defocus in animal models of myopia across numerous species.[16–20] A smaller pupil size and the absence of accommodative errors may contribute to an improved retinal image during distance viewing. In animal models, the absence of defocus can have a powerful inhibitory effect on growth toward excessive myopic ocular lengths.[19, 21] Alternatively, the greater amount of light outdoors may alter retinal levels of dopamine, also shown to inhibit myopic ocular growth.[22–23]

Another possibility is that the protective effect of time outdoors is from higher levels of cutaneously-derived vitamin D. Several lines of evidence are consistent with this hypothesis. Chief among these is the finding that time outdoors rather than any specific physical activity carries the protective effect.[13–14] There are also seasonal effects on eye growth, resulting in a faster rate of myopia progression in the autumn and winter when there are fewer hours of daylight and a slower rate in the sunnier spring and summer months.[24] The purpose of this study was to evaluate whether myopic and non-myopic individuals differ with respect to circulating levels of vitamin D, with appropriate adjustment for activities or dietary factors that might affect vitamin D.

METHODS

The research followed the tenets of the Declaration of Helsinki. All subjects signed written consent documents after being informed of the purposes of the study including its risks and benefits. Any child under the age of 18 years signed an assent form and the parent or guardian signed the consent form. Recruitment was through email or word of mouth, either sent by the Worthington (Ohio) City Schools to parents of high school age children inviting them to participate in the study or by the investigators to optometry students at Ohio State. A total of thirty-two subjects were examined between the ages of 13 and 25 years of age, with no regard to gender or ethnicity. Subjects were tested between December 2008 and September 2009. Hours of daylight were calculated for each day of testing using data obtained from the National Oceanic and Atmospheric Administration (http://www1.ncdc.noaa.gov/pub/data/ccd-data/CCD-2008.pdf). Subjects were excluded if they had any significant history of ocular disease, strabismus, refractive surgery, or therapies for myopia including corneal reshaping, bifocals, or the use of atropine. Subjects with any systemic disease associated with myopia, such as diabetes, Marfan's syndrome, and Down's syndrome were also excluded. Best corrected visual acuities were required to be 6/7.5 or better in each eye. Nineteen females and 13 males were seen with a mean age of 19.8 ± 4.6 years.

Two drops of tropicamide 1.0% were instilled into each eye separated by five minutes to obtain cycloplegia following a thirty minute period.[25] During cycloplegia, subjects answered questions from two surveys read to them by an investigator. The first was a modified World Health Organization Refractive Error Study in Children visual activity survey and the other was the Block Kids Food Frequency Questionnaire (FFQ) version 2004 for children ages 8–17 (NutritionQuest, Berkeley, CA; http://www.nutritionquest.com). Following survey completion and thirty minutes of cycloplegia, subject's refraction was measured on a Grand Seiko WR-5100K. Subjects were classified as myopic, ineligible (emmetropic, borderline myopic, astigmatic, or anisometropic), or non-myopic based on an average of ten readings from auto-refraction. Myopes had at least −0.75D of myopia in each principal meridian (n=14). Non-myopes had at least +0.25D or more hyperopia in each principal meridian (n=8). Subjects failing to fall into either the myope or non-myope categories were ineligible (n=10) and were not tested or analyzed further. Refractive error was treated as a categorical rather than as a continuous variable because of the assumption that time outdoors was related to the risk of onset[2] but not to the rate of progression and, therefore, not to the degree of myopia.26

The WHO RESC activity survey was modified slightly to better represent typical American activities and nomenclature. Questions related to specific activities or just to time spent in no particular activity were converted to hours per day and then categorized into whether the time was spent indoors or outdoors. Relevant activities were also broadly categorized as either close work (homework, leisure reading, computer work) or sports (exercise and athletic participation). School days or work days were assessed separately from non-school or non-work days. When added together, these sums formed the variables *Total Outdoors*, *Total Indoors*, *Total Close Work*, and *Total Sports*. The Block Kids FFQ 2004 uses a series of 77 food items to determine how often a particular food or group of foods was consumed in the past week and the portion eaten each day. Food frequency questionnaires are one of several methods for dietary data collection including 24-hour recall and food diaries. While FFQs are the more widely used method because of ease of administration and low cost, their validity is considered slightly poorer compared to 24-hour recall.[27] However in a study of adults 20–70 years of age, the Block FFQ compared well to 24-hour recall data and to a more extensive 36-page 124-item FFQ.[28] The Block Kids FFQ took about 25 minutes to complete. The completed surveys were sent to NutritionQuest for analysis of levels of nutrients consumed in each subject's diet.

Peripheral blood samples were collected using a sterile single-use 1.5 mm-wide spring-loaded lancet (Sarstedt Inc.) following disinfection of the site using an isopropyl alcohol pad. Blood was collected in a Sarstedt Microvette 200 capillary tube with heparin as the anticoagulant. Each eligible subject gave approximately 200μl of blood which was stored at −87°C. The 22 samples of blood were sent to The Ohio State University Comprehensive Cancer Center Pharmacoanalytical Shared Resource for analysis of blood level of 25(OH) vitamin D_3 by liquid chromatography coupled with mass spectrometry. The 25(OH) vitamin D_3 was separated by a high performance liquid chromatography system (Shimadzu HPLC system, Shimadzu, Columbia, MD) and protonated to the ionic form to be detected by a triple quadrupole mass spectrometer (Finnigan TSQ Quantum EMR Triple Quadrupole mass spectrometer, Thermo Fisher Scientific, San Jose, CA). One-hundred microliter samples of whole blood were analyzed with insertion of intermittent quality control samples to ensure data quality (precision and accuracy <±15%). Statistical analysis was performed using PASW software (SPSS Inc, Chicago, version 17.0).

RESULTS

Demographic data for myopes and non-myopes are given in Table 1. There were no significant differences in age between the two groups and the proportion of males and females was similar. None of the variables for time spent indoors, outdoors, close work, sports, or blood level of vitamin D was different between myopes and non-myopes. This small sample of myopes did not spend a greater amount of time reading or lower amount of time outdoors, characteristics reported from other samples of myopes compared to non-myopes.[7–10, 12–14]

Blood levels of vitamin D were not correlated with time spent outdoors ($r = -0.03$, $p = 0.91$). The expected positive correlation between hours of daylight and blood vitamin D[29–30] was not significant in this small sample ($r = 0.24$, $p = 0.29$). There were no significant differences in the hours of daylight during testing for myopes and non-myopes ($p = 0.20$) nor was there a significant correlation between hours of daylight and time spent outdoors ($r = 0.10$, $p = 0.58$). Blood levels of vitamin D were correlated with several of the 49 nutritional variables (Table 2). Greater dietary intake of carbohydrate, sugar, folate in food and total folate (from food plus supplements), and vitamin B_6 were associated with lower blood levels of vitamin D. Neither dietary intake of vitamin D (including supplements, $p = 0.74$) nor calcium ($p = 0.12$) were correlated with blood levels of vitamin D in this sample. Each of the 49 different dietary variables was placed into one-way ANOVAs comparing mean levels of each nutrient between myopes and non-myopes. Five nutrients were significantly different at the 0.05 level (Table 3). None of these variables were ones that had any significant correlation with blood levels of vitamin D. By the same token, variables that were correlated with blood levels of vitamin D were not significantly different between myopes and non-myopes (Table 3).

Each of the variables in Tables 2 and 3 associated with either vitamin D or myopia was evaluated in the multivariate regression model with blood level of vitamin D as the dependent variable. The terms in the model were chosen through a backward selection process that placed all terms in an initial model, then removed terms one-by-one beginning with the least significant term. Terms remained in the model if their removal resulted in a significantly poorer fit to the data. While this approach to model fitting might be considered more aggressive than a traditional forward stepwise approach, it should be seen as exploratory considering the limited literature on nutrition, particularly vitamin D, and myopia. Total sugar (rather than carbohydrate) and food folate (rather than total folate) remained significantly related to blood levels of vitamin D. Vitamin B_6 was not significant in this multivariate model. Calcium became significantly related to blood levels of vitamin D in the multivariate model with total sugar and food folate in contrast to its lack of significance as a univariate term, but dietary vitamin D was still not significant. Again in exploratory modeling, each remaining dietary variable was assessed one-by-one by placement in a multivariate model alongside total sugar, food folate, and calcium. Theobromine was significantly related to blood levels of vitamin D in this multivariate model. As a single variable, theobromine was not significantly correlated with blood level of vitamin D ($p = 0.30$) nor was it different between myopes and non-myopes ($p = 0.26$).

Myopia status (myopic or non-myopic), age, and gender were then evaluated in this base model of total sugar, food folate, calcium, and theobromine where blood level of vitamin D was the dependent variable. Myopia status and age were significant, but not gender. The final model coefficients are given in Table 4. Consumption of food folate and sugar was related to lower blood levels of vitamin D while consumption of calcium and theobromine, in addition to older age, was related to higher blood levels of vitamin D. The use of sunscreen and hours of daylight did not affect these results ($p = 0.90$ and $p = 0.09$, respectively). Adjusted for age and dietary factors, myopes had a lower blood level of vitamin D by 3.4ng/ml (estimated mean for myopes = 13.5ng/ml, non-myopes = 16.9ng/ml). The final model adjusted R^2 was high at 0.76.

DISCUSSION

The primary hypothesis that the study set out to evaluate was whether the documented protective effect of time outdoors for myopia might operate through modulation of the blood level of cutaneously-derived vitamin D. This hypothesis could not be evaluated fully as there was no significant effect of time outdoors as a function of refractive error in this small sample. The finding that myopes have lower circulating levels of vitamin D than non-myopes is at least consistent with this hypothesis. Differences in circulating vitamin D without differences in time spent outdoors may actually be a more interesting finding, more indicative of intrinsic differences in vitamin D metabolism between myopes and non-myopes. Future work in a larger sample that displays the outdoor effect in myopia will be needed to determine the effects of environment (time outdoors and diet), the differences in vitamin D in myopes that are independent of environment, and whether these differences might play any plausible role in the development of refractive error. A larger sample size would also allow for analyses of refractive error as a continuous variable.

Several dietary variables were found to be related to blood levels of vitamin D. The positive association between increased calcium in the diet and increased vitamin D levels in the blood is consistent with a published report.[30] Lower levels of vitamin D have been found in the obese and the obese have greater carbohydrate intakes,[31] but the inverse relationship between total sugar intake and vitamin D has not been reported to our knowledge. Folate is found in leafy vegetables like spinach, beans, and citrus and is responsible for several beneficial functions including DNA repair, maintaining the integrity of rapidly dividing cells, and prevention of neural tube defects.[32] The inverse relationship between folate intake and blood vitamin D levels is somewhat disturbing if both nutrients are supposed to be beneficial. An inverse relationship between folate and vitamin D does have some precedent, however, at least in the skin; skin folate levels are degraded by ultraviolet exposure.[33] Recent speculation about the evolution of human skin pigmentation describes a sort of “push-pull” relationship between having enough pigmentation to protect systemic levels of ultraviolet-sensitive folate, but not too much given the prevailing UV environment to inhibit sufficient synthesis of vitamin D.[31] Theobromine is an alkaloid similar to caffeine found in tea, cola, and chocolate.[34] There is no obvious connection between intake of theobromine and blood level of vitamin D.

Higher blood levels of vitamin D have been reported to be associated with more time outdoors,[29,35] and to higher dietary intake of vitamin D,[30,36–37] but these relationships were not found in the current study. The small sample size and limited statistical power is a likely explanation. Dietary sodium was also not related to blood levels of vitamin D, in contrast to a previous report on postmenopausal Brazilian women with osteoporosis.[38] A previous study in Hong Kong found certain dietary nutrients to be different between non-myopic children and those who became myopic (protein, fat, vitamin B_1, vitamin C, iron, and cholesterol).[39] None of the nutrients related to blood levels of vitamin D (Table 2) or that were significantly different between myopes and non-myopes (Table 3) were common to the two studies. Further work will have to determine whether these differences between studies were due to the Asian ethnicity of the subjects in the previous study, that they were younger in age (7 to 10 years old), or due to some other factor.

No published studies have investigated any physiologic connection between myopia and a protective effect of vitamin D. There are a few possible avenues to pursue. Vitamin D is known to be a powerful regulator of cellular differentiation with strong anticancer and antiproliferative effects.[40] Perhaps there are direct, antiproliferative effects of vitamin D on scleral growth that could be influential in regulating the length and refractive error of the eye. Growth regulation might also involve retinoic acid, a bi-directional regulator of eye growth in animal models of myopia.[41–42] Retinoic acid and vitamin D engage in some crosstalk in signaling and cell-cycle regulation through overlapping binding specificities.[43] Vitamin D and myopia may also be related by the recent finding that the ciliary smooth muscle of the eye is larger in myopic children.[44] Ciliary muscle enlargement may have functional and structural consequences for the eye that increase myopia risk.[45] Vitamin D may be beneficial to the function of smooth muscle. Longitudinal epidemiologic results have shown that a greater dietary intake of vitamin D is associated with a reduced risk of overactive bladder, a condition characterized by poorly functioning hypertrophic smooth muscle.[46] Speculating further on potential connections between vitamin D and myopia, the prevalence of myopia appears to be on the rise in Asian populations[47] at the same time that traditional sources of vitamin D from fish may be being replaced by other sources of protein and calories in the Asian diet.[48] In Taiwan, for example, males aged 45–64 years have a dietary intake of 3.39 µg/day of vitamin D from fish, but 6–12 year old boys only obtain 1.74 µg/day from this major food source of vitamin D.[49] The prevalence of myopia in the US has also been reported to have increased in the last 30 years, from 25% in 1971–1972[50] to 33% in 1999–2004[51] as deficiencies in vitamin D become more common.[37,52] Again, further research in these areas would be needed to identify whether relevant biological connections exist between myopia and vitamin D.

These results may be considered moderate in terms of effect size. Myopes had lower blood levels than non-myopes by 3.4ng/ml when the average serum level is about 25ng/ml with a standard deviation on the order of 8–12ng/ml.[53] It should be noted that this first iteration assay technique used whole blood from the subject when the serum or plasma concentration would be more appropriate. Blood levels of vitamin D may be 67% of plasma levels given that vitamin D is not found in erythrocytes.[54] When adjusted by this factor, the plasma vitamin D levels in myopes may be 5.1ng/ml lower than in non-myopes when converted from blood levels, a difference of about a 20% between refractive error groups if 25ng/ml is considered average. Put on another scale, this difference is about half that of the effect reported for changing season from summer to winter.[30] Over 500 IU per day might be required to close this deficit through dietary supplementation.[55]

This study has several limitations, the primary one being its small sample size. A small sample size may have limited the statistical power to find effects related to time outdoors and some other highly probable effects, such as dietary intake of vitamin D. On the other hand, the level of statistical significance for refractive error group and the very high overall adjusted R^2 found at this sample size give some indication that the differences in vitamin D levels between refractive error groups may be very robust. Replication studies will be needed to confirm this finding. Another limitation is the aggressiveness of the modeling used to identify significant dietary variables that very likely increased chances of a type I error beyond the 0.05 level. Future work of this kind will also be useful in determining whether the relationships found in this exploratory analysis are false positives or reproducible findings.

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Table 1

Descriptive statistics for the myopic cases and non-myopic control subjects. Ineligible subjects (emmetropic, borderline myopic, astigmatic, or anisometropic) had an average ±SD refractive error of −0.18 ± 0.62D.

	Myopes n = 14	**Non-Myopes n = 8**	**p-value**
Age	20.15 ± 5.42	18.68 ± 3.63	0.46
Gender			
Female	n = 6	n = 5	
Male	n = 8	n = 3	
Spherical Equivalent Refractive Error (D)	−3.18 ± 1.45	+0.88 ± 0.26	NA
Total Outdoors (hrs/wk)	12.9 ± 7.78	13.6 ± 5.77	0.83
Total Indoors (hrs/wk)	112 ± 18.1	112 ± 11.7	0.90
Total Close Work (hrs/wk)	37.8 ± 14.0	35.6 ± 9.08	0.68
Total Sports (hrs/wk)	5.82 ± 3.72	8.56 ± 7.18	0.34
Total Dietary Vitamin D (IU/day)	261 ± 215	190 ± 177	0.44
Blood Vitamin D (ng/ml)	13.9 ± 3.75	16.0 ± 5.11	0.29

Table 2

Significant univariate correlations (Pearson coefficients) between dietary nutrient variables and blood levels of vitamin D.

Dietary Nutrient	Correlation	p-value
Carbohydrate (g)	−0.59	0.004
Sugars—Total (g)	−0.54	0.009
Food folate (μg)	−0.47	0.028
Total folate/folic acid (μg)	−0.45	0.035
Vitamin B_6 (mg)	−0.45	0.036

Table 3

Significant univariate dietary differences between myopes and non-myopes. Non-significant results for the dietary variables related to blood levels of vitamin D from Table 2 are also displayed.

Dietary Nutrient	Myopes	Non-Myopes	p-value
Fiber (g)	13.6 ± 3.62	9.26 ± 3.03	0.009
Copper (mg)	0.98 ± 0.17	0.73 ± 0.22	0.009
Natural folate (μg)	178 ± 58.9	120 ± 49.3	0.024
Magnesium (mg)	210 ± 51.7	153 ± 41.9	0.016
Solid food weight (g)	713 ± 183	530 ± 188	0.037
Carbohydrate (g)	200 ± 41.9	182 ± 34.9	0.34
Sugars—Total (g)	98.6 ± 28.5	95.9 ± 25.8	0.82
Food folate (μg)	323 ± 71.6	310 ± 100	0.73
Total folate/folic acid (μg)	423 ± 99.1	443 ± 160	0.72
Vitamin B_6 (mg)	1.47 ± 0.35	1.37 ± 0.54	0.60

Table 4

Multivariate linear regression parameter estimates of factors related to blood levels of vitamin D. Coefficients are the difference in vitamin D level (ng/ml) per unit difference for each factor, adjusted for all other terms in the table. Adjusted model $R^2 = 0.76$.

Factor	Coefficient	p-value
Diet		
Food folate (per μg/day)	−0.035	0.001
Sugars—Total (per g/day)	−0.12	0.001
Calcium (per mg/day)	0.010	0.006
Theobromine (per mg/day)	0.10	<0.0001
Demographic		
Age (per year)	0.32	0.026
Case Status		
Myopic (ng/ml lower)	−3.4	0.005