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Low Serum 25-Hydroxyvitamin D Is Associated With Myopia in Korean Adolescents

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Purpose. To assess the relationship between serum level of 25-hydroxyvitamin D (25(OH)D) and refractive error in Korean adolescents.

Methods. A total of 2038 adolescent aged 13 to 18 years, who participated in the Korea National Health and Nutrition Examination Survey (KNHANES) from 2008 to 2011 underwent refractive examination using an autorefractor. Serum 25(OH)D concentration and other potential risk factors were examined. Multivariate regression analysis was performed to investigate the association between serum 25(OH)D and spherical equivalent (SE).

Results. Among the participants, 80.1% had myopia (−0.5 diopters [D] or more myopic) and 8.9% had high myopia (−6.0 D or more myopia). Age, total energy/Ca intake, area of residence, parental income, and smoking experience were significantly different among groups according to SE (All, $P < 0.05$). The age-adjusted distribution of SE according to serum 25(OH)D concentration showed a positive relationship ($r = 0.067$, $P = 0.012$). The myopia group had a significant positive relationship between SE and serum 25(OH)D tertile concentration ($P = 0.020$), whereas the nonmyopia group did not have any significant relationship ($P = 0.599$). In multiple linear regression analyses, SE was significantly associated with low serum 25(OH)D concentration after adjustment for area of residence, parental income, total energy intake, dietary Ca intake, milk consumption, and smoking experience ($P = 0.047$). The prevalence of high myopia was significantly associated with the lowest tertile of serum 25(OH)D concentration after adjustment for the confounding factors ($P = 0.017$).

Conclusions. Low serum 25(OH)D concentration was associated with myopia prevalence in Korean adolescents. This relationship was particularly notable in adolescents with high myopia.

Keywords: myopia, vitamin D, 25-hydroxyvitamin D

Myopia has emerged as a major health issue worldwide, and its prevalence has increased rapidly in the past few decades, particularly in East Asia.[1] In a previous study on Singapore military conscripts, the myopia rate was noted as 81.3% in 2009.[1] In a study reporting the prevalence of major eye disease in Korea, the prevalence of myopia was greatest in those aged 12 to 18 years (78.8%), followed by 19 to 29 years (75.3%).[2] In a recent study on 19-year-old males in Korea, the prevalence of myopia was even higher, at 96.5%.[3] Due to the sharp myopic shift in the young generation of urban East Asian and Southeast Asian populations, research has focused on factors that could increase the risk of myopia.[1] Although the causes of myopia are unclear, numerous studies have suggested it to be associated with parental myopia,[4,5] near work,[4,6] school achievements, and urbanization.[6,7] Recently, time spent in outdoor activities has been recognized as a protecting factor against myopia.[7,8] It is well established that increasing time spent outdoors is associated with less myopia,[6,8–11] although there is controversy about the association of time spent outdoors and the myopia progression.[12–14]

Considering that vitamin D is synthesized endogenously from exposure to sunlight, it may serve as a biomarker of outdoor activity.[15] Furthermore, polymorphisms within vitamin D receptor (VDR) are associated with a low to moderate degree of myopia; SNP (single nucleotide polymorphism) rs1635529 on chromosome 12, region q13.11, which is in the vicinity of the genes of VDR, showed highly significant over transmission to myopic individuals in families participating in the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study.[16]

Despite the proposed role of vitamin D in myopia, no previous population-based study has performed the prevalence of myopia in association with blood levels of vitamin D. The prevalence of vitamin D deficiency has increased worldwide during the past few decades.[15,17,18] A Korean nationwide survey conducted in 2008 revealed that vitamin D insufficiency (<20 ng/mL) was 55.9%, with the most common cases occurring in the younger generation.[19] Korean adolescents are especially reported to be at increased risk for vitamin D insufficiency, which may be related to high latitude (34°–38° N), increased use of sunscreen, reduced outdoor activity due to

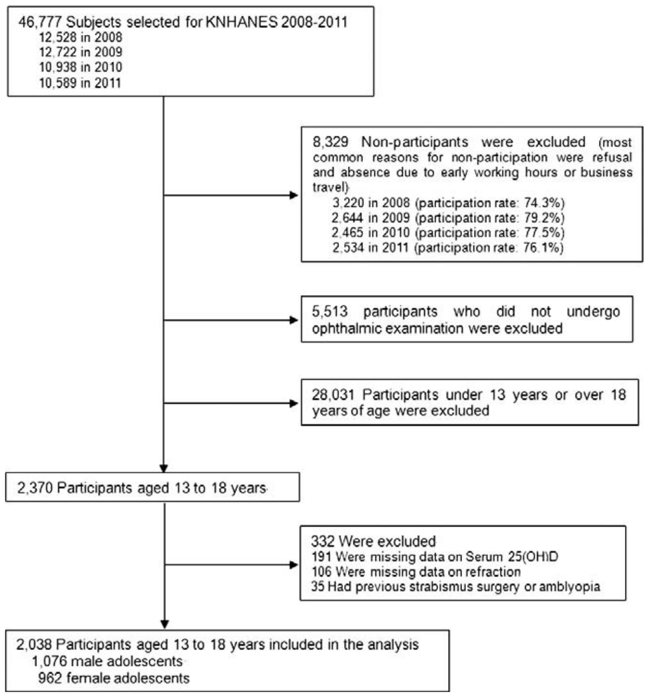

Figure 1. Flow diagram presenting the selection of study participants.

high educational pressure, and lack of vitamin D–fortified foods.[19,20] In this regard, it is hypothesized that low vitamin D status may play a significant role in the development of myopia in adolescence; a critical period for bone accretion and growth.[21] Therefore, in this study, we focused on the relationship between blood level of 25-hydroxyvitamin D (25(OH)D) and refractive error in Korean adolescents.

Methods

Data Source and Participants

The Korea National Health and Nutrition Examination Survey (KNHANES) is a nationwide, population-based, and cross-sectional health examination and survey regularly conducted by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention, Ministry of Health and Welfare, to monitor the general health and nutritional status of people in South Korea. To date, KNHANES has been performed in 1998 (KNHANES I), 2001 (KNHANES II), 2005 (KNHANES III), 2007 to 2009 (KNHANES IV), and 2010 to 2012 (KNHANES V). It consists of a health interview survey, a nutrition survey, and a health examination survey. A stratified, multistage probability sampling design is used for the selection of household units that participate in the survey. Additional details regarding the study design and methods are provided elsewhere.[22,23]

Data from the fourth (KNHANES IV-2&3, 2008, 2009) and fifth (KHANES V 1&2, 2010, 2011) studies were used to estimate the association between serum 25(OH)D and refractive error (the mean age of study population; 38.3 ± 0.2 year [3–97 years]). Among 30,401 participants, 2370 individuals aged 13 to 18 years were selected for the current study. Among these, 232 were excluded: 191 had missing 25(OH)D values, 106 had missing data for refractive error, and 35 had ocular pathology (presence of strabismus or amblyopia). A final 2038 participants (1076 male and 962 female adolescents) aged 13 to 18 years were used in this analysis as shown in Figure 1. The KNHANES IV and V studies were conducted according to the guidelines laid down in the Declaration of Helsinki. All participants in the survey signed an informed consent form. The institutional review board of St. Vincent Hospital, College of Medicine, the Catholic University of Korea (Seoul, Korea) approved the protocol.

Participant Data and Measurements

As a part of a standardized ophthalmic examination conducted by epidemiologic survey members of the Korean Ophthalmologic Society, all participants underwent noncycloplegic autorefraction of both eyes using a nonaccommodative picture target with standard background illumination on the Topcon KR8800 autorefractor (Topcon, Tokyo, Japan). Spherical equivalent (SE) refractive error was calculated as sphere +1/2 cylinder. Myopia was defined by an SE of −0.50 diopters (D) or more myopic. Mild myopia was defined as greater than −3.0 D; moderate myopia was defined as less than or equal to −3.0D; and high myopia was defined as less than or equal to −6.0 D.

Demographic variables, include age, sex, area of residence, parents' income, alcohol drinking, and smoking experience. Area of residence was categorized as urban and rural region. Among the 16 districts of South Korea, eight major cities (Seoul, Gyeonggi, Busan, Daegu, Incheon, Gwangju, Daejeoun, and Ulsan) were grouped as urban areas, and the other provinces (Gangwon, Chungbuk, Chungnam, Jeonbuk, Jeonnam, Gyeongbuk, Gyeongnam, and Jeju) were grouped as rural areas. Participants were categorized in the low-income group if their parents' income belonged to the lowest quartile. Regarding alcohol drinking, subjects were subdivided into two groups based on the frequency of drinking for the past year: less than once per month, and at least once per month (once per month or more than once per month). Smoking was defined as the presence of any experience of smoking in the past (former smoker) or 1 or more day(s) of smoking in the past 30 days (present smoker).

Nutrient intakes, including total energy and Ca intakes, were assessed with a 24-hour dietary recall questionnaire administered by a trained dietician. Dietary and supplemental Ca intakes were compared with the dietary reference intake (DRI) for Ca of Korean children and adolescents: 1000 mg/d for boys aged 12 to 14 years, 900 mg/d for girls aged 12 to 14 years, 900 mg/d for boys aged 15 to 18 years, and 800 mg/d for girls aged 15 to 18 years.[24] Calcium intake levels were categorized into two groups: greater than or equal to the DRI and, less than the DRI. A qualitative food frequency questionnaire (FFQ) was used to collect the dietary information with food items described into 10 categories: (1) never or seldom, (2) six to 11 times per year, (3) once per month, (4) two to three times per month, (5) once per week, (6) two to three times per week, (7) four to six times per week, (8) once per day, (9) twice per day, (10) and three times per day. To adjust for the dietary source of vitamin D, we compared the consumption frequencies of milk and fish, which were associated with the serum 25(OH)D concentrations in Korean adolescents.[25] Subjects were subdivided into two groups based on the consumption frequency of milk and fish: at least once per week, or less than once per week.

Physical activity was measured by self-report using the International Physical Activity Questionnaire.[26] Moderate physical activity was categorized as "yes" when participants engaged in moderate-intensity physical activity for more than 20 minutes at a time and more than 3 times/wk. Moderate-intensity physical activity was defined as the physical activity that causes a slight increase in breathing or heart rate for at least 10 minutes, such as when carrying light loads, cycling at a regular pace, or playing tennis.

Anthropometric measurements were performed by a specially trained examiner. Waist circumference was measured to the nearest 0.1 cm in a horizontal plane at the level of the midpoint between the iliac crest and the costal margin at the end of normal expiration. Body mass index (BMI) was calculated as the individual's weight in kilograms divided by the square of the individual's height in meters.

Serum 25(OH)D Measurements

Serum levels of 25(OH)D were assayed according to an agreed protocol. Overnight fasting–blood samples were collected from each participant during the survey, and serum 25(OH)D levels were measured by radioimmunoassay (DiaSorin, Stillwater, MN, USA) using a gamma counter (1470 Wizard; Perkin Elmer, Turku, Finland). The interassay coefficients of variation (CV) were 2.8% to 6.2% for 2008 to 2009 samples and 1.9% to 6.1% for 2010 to 2011 samples. The KNHANES study participates were evaluated via the Vitamin D Standardization Program, so the measurement of 25(OH)D was standardized with the recently developed National Institute of Standards and Technology-Ghent University reference procedure.[27] Subjects were categorized into tertiles (T) of vitamin D and with cut-off values, which were determined separately for male and female adolescents.

Statistical Analyses

Statistical analyses were performed using the SAS survey procedure (version 9.2; SAS Institute, Inc., Cary, NC, USA) to reflect the complex sampling design and sampling weights of KNHANES and to provide nationally representative prevalence estimates. The procedures included unequal probabilities of selection, oversampling, and nonresponse so that inferences could be made about the Korean adolescent participants.

Participants' characteristics were described using means and standard errors for continuous variables and numbers and percentages for categorical variables according to the SE. The association in refractive error across the tertiles of serum 25(OH)D concentration was also examined in the myopia group and the nonmyopia group.

Simple and multiple linear regression analyses were used to examine the association between serum 25(OH)D concentration and SE. First, we adjusted for age and sex (Model 1). We then adjusted for age, sex, and other confounders that showed differences of borderline significances ($P < 0.250$) according to the SE (Model 2). In myopic population (SE –0.50 D or more myopic), a multiple logistic regression analysis were also performed to compare the odds of being high myopia (a group with the upper tertile of serum 25(OH)D versus a group with the lower tertile of serum 25(OH)D). For all analyses, P values were two-tailed and less than 0.05 was considered to indicate statistical significance.

Results

Among the study participants, 80.1% had myopia (–0.5 D or more myopic) and 8.9% had high myopia (–6.0 D or more myopia). The proportion of wearing correction glasses was 45.3%. Spherical equivalence in the right and left eyes was highly correlated (Pearson's correlation = 0.91, $P < 0.001$). Therefore, only data for the right eyes were presented.

The clinical characteristics according to grade of myopia are shown in Table 1. The study participants were aged 15.4 ± 0.1 years in the nonmyopia group, 15.5 ± 0.1 years in the mild myopia group, 15.5 ± 0.1 years in the moderate-myopia group, and 16.0 ± 0.1 years in the high-myopia group ($P < 0.001$). The proportion of wearing correction glasses was 6.4 ± 1.9% in nonmyopia, 21.9 ± 1.7% in mild myopia, 83.4 ± 1.8% in moderate myopia, and 92.9 ± 2.4% in high myopia ($P < 0.001$). Body heights were 165.7 ± 0.5 cm in the nonmyopia group, 166.5 ± 0.4 cm in the mild-myopia group, 166.3 ± 0.4 cm in the moderate-myopia group, and 168.2 ± 0.7 cm in the high myopia group ($P = 0.019$). The weight, BMI, and waist circumference were not significantly different among the groups ($P = 0.421$, 0.778, and 0.480, respectively). The serum 25(OH)D concentrations were 16.3 ± 0.3 ng/mL in the nonmyopia group, 16.4 ± 0.3 ng/mL in the mild-myopia group, 16.0 ± 0.3 ng/mL in the moderate-myopia group, and 15.2 ± 0.4 ng/mL in the high-myopia group ($P = 0.054$). Daily total energy intake and daily Ca intake were significantly different among the groups ($P = 0.025$ and 0.028). Consumption frequencies of milk and fish were not significantly different among the groups ($P = 0.174$ and 0.748).

Frequency of rural residence differed significantly according to the degree of myopia ($P = 0.008$). The frequency of regular physical activity did not differ significantly among the groups ($P = 0.622$). The frequency of low parental income differed significantly according to the degree of myopia ($P = 0.004$). The proportion of smoking experience was 24.5 ± 0.7% in nonmyopia, 24.2 ± 0.8% in mild myopia, 17.0 ± 0.6% in moderate myopia, and 11.1 ± 0.3% in high myopia ($P = 0.002$).

The distribution of refractive error (SE) according to the serum 25(OH)D concentration is shown in Figure 2. There was a positive relationship between serum 25(OH)D concentration and SE after adjustment for age ($r = 0.067$, $P = 0.012$). Figure 3 shows that the myopia group had a significant positive relationship between SE and serum 25(OH)D tertile concentration ($P = 0.020$), whereas the nonmyopia group did not have any significant relationship ($P = 0.599$). Tertile cutoff values of 25(OH)D (ng/mL) were T1 less than 13.83, T2 13.83 to less than 18.37, T3 greater than or equal to 18.37 for male adolescents, and T1 less than 13.01, T2 13.01 to less than 16.99, T3 greater than or equal 16.99 for female adolescents.

The results of multiple linear regression analyses are shown in Table 2. The SE was significantly associated with low serum 25(OH)D concentration after adjustment for age and sex ($P = 0.012$), which was maintained after adjustment for age, sex, area of residence, parental income, total energy intake, milk consumption, daily calcium intake, and smoking experience ($P = 0.047$).

To assess the impact of serum 25(OH)D on degree of myopia, the myopia group was categorized further into low to moderate myopia (–0.5 to –6.0 D) and high myopia (<–6.0 D) (Table 3). Multiple logistic regression analysis revealed that the prevalence of high myopia was significantly associated with serum 25(OH)D tertiles after adjustment for age and sex ($P = 0.016$), which was maintained after adjustment for age, sex, area of residence, parental income, total energy intake, milk consumption, daily Ca intake, and smoking experience ($P = 0.017$). Especially the odds of being high myopia in a group with the upper tertile of serum 25(OH)D were significantly lower than those in a group with the lower tertile of serum 25(OH)D (odds ratio [OR]: 0.55; 95% confidence interval [CI]: 0.34, 0.90).

Discussions

We found a significant association between low serum 25(OH)D concentration and myopia in Korean adolescents aged 13 to 18 years. Serum 25(OH)D concentration was an independent predictor of refractive error after adjustment for potential confounding factors such as age, sex, area of

TABLE 1. Clinical Characteristics of Study Subjects According to the Spherical Equivalent in Korean Adolescents ($n = 2038$)

	Nonmyopia SE > −0.5 D	Mild Myopia −3.0 D < SE ≤ −0.5 D	Moderate Myopia −6.0 D < SE ≤ −3.0 D	High Myopia SE ≤ −6.0 D	P Value
Numbers	405 (19.9%)	855 (41.9%)	596 (29.2%)	182 (8.9%)	
Age, y	15.4 ± 0.1	15.4 ± 0.1	15.5 ± 0.1	16.0 ± 0.1	<0.001
Sex, % of male	52.7 ± 1.3	55.3 ± 0.9	51.5 ± 1.1	53.3 ± 0.6	0.678
Spherical equivalent, D	0.3 ± 0.1	−1.6 ± 0.0	−4.2 ± 0.0	−7.4 ± 0.1	<0.001
Wearing of correction glasses, %	6.4 ± 1.9	21.9 ± 1.7	83.4 ± 1.8	92.9 ± 2.4	<0.001
Height, cm	165.7 ± 0.5	166.5 ± 0.4	166.3 ± 0.4	168.2 ± 0.7	0.019
Weight, kg	58.3 ± 0.9	59.4 ± 0.5	58.7 ± 0.6	60.1 ± 1.0	0.421
BMI, kg/m^2	21.1 ± 0.3	21.3 ± 0.1	21.1 ± 0.2	21.2 ± 0.3	0.778
Waist circumference, cm	71.1 ± 0.6	71.7 ± 0.4	70.9 ± 0.5	71.7 ± 0.8	0.480
Serum 25(OH)D concentration, ng/mL	16.3 ± 0.3	16.4 ± 0.3	16.0 ± 0.3	15.2 ± 0.4	0.054
Total energy intake, kcal/d	2085.8 ± 68.9	2178.9 ± 44.3	2196.6 ± 44.0	1959.8 ± 71.5	0.025
Energy from fat, %	22.8 ± 0.6	22.2 ± 0.4	23.2 ± 0.5	23.0 ± 0.7	0.440
Energy from carbohydrate, %	62.9 ± 0.6	63.6 ± 0.5	62.5 ± 0.5	62.6 ± 1.0	0.512
Energy from protein, %	14.2 ± 0.3	14.2 ± 0.2	14.3 ± 0.2	14.4 ± 0.4	0.962
Daily Ca intake ≥ DRI, %	8.3 ± 1.8	10.4 ± 1.4	13.9 ± 1.9	5.3 ± 1.8	0.028
Milk consumption ≥ 1/wk, %	29.0 ± 2.9	30.7 ± 1.9	36.5 ± 2.6	31.2 ± 4.3	0.174
Fish consumption ≥ 1/wk, %	18.6 ± 2.5	19.0 ± 1.6	19.0 ± 2.0.	22.9 ± 3.2	0.748
Area of residence, % of rural regions	18.5 ± 0.7	20.8 ± 1.2	11.6 ± 0.6	15.1 ± 0.3	0.008
Low income, %	21.9 ± 0.7	16.3 ± 0.7	11.2 ± 0.5	11.7 ± 0.36	0.004
Smoking experience, %	24.5 ± 0.7	24.2 ± 0.8	17.0 ± 0.6	11.1 ± 0.3	0.002
Alcohol drinking, %	32.8 ± 0.8	31.9 ± 0.9	28.7 ± 0.7	36.3 ± 0.5	0.391
Regular physical activity, %	30.5 ± 0.7	27.9 ± 0.8	25.7 ± 0.7	27.5 ± 0.4	0.622

Data are presented as the means ± standard error, or percent ± standard error.

residence, parental income, total energy intake, milk consumption, daily Ca intake, and smoking experience (Table 2). The association between serum 25(OH)D and refractive error was significant particularly in the high-myopia group (Table 3). Consistent with our study, Mutti and Marks[28] reported that blood vitamin D level in myopia was lower than in the absence of myopia. To our knowledge, however, this is the first large scale, population-based study on the association between serum vitamin D concentration and refractive error in adolescents using nationally representative data.

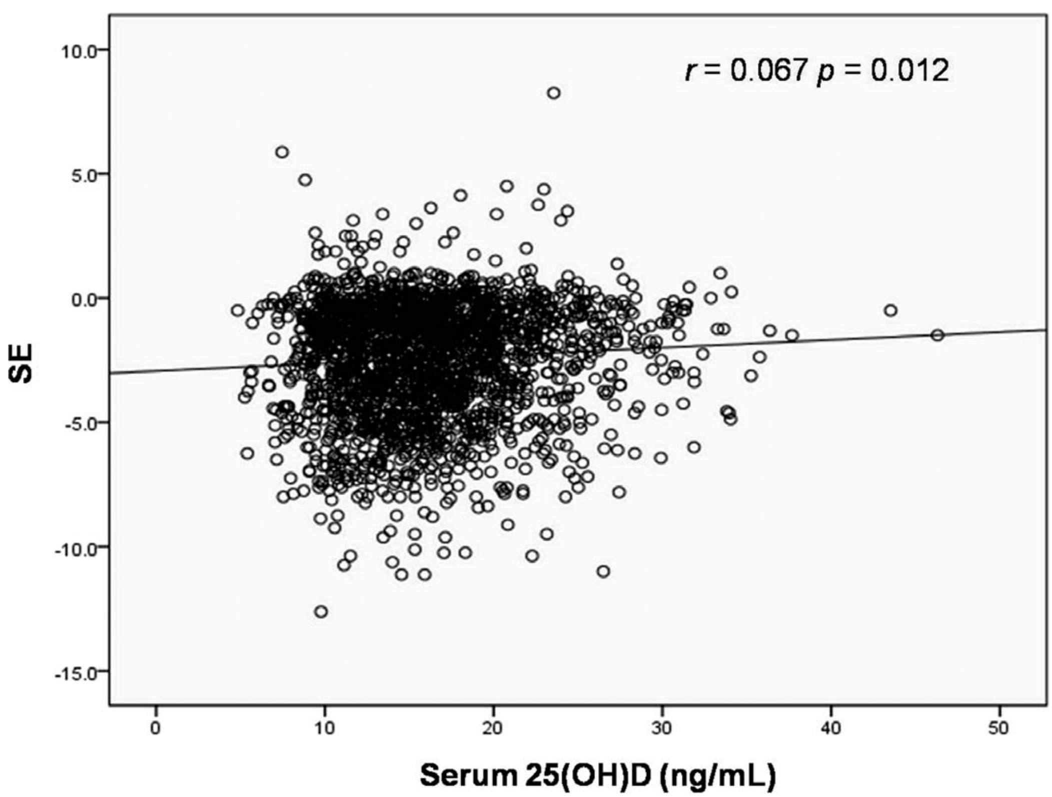

FIGURE 2. The distribution of refractive error according to the serum 25(OH)D concentration for the whole population.

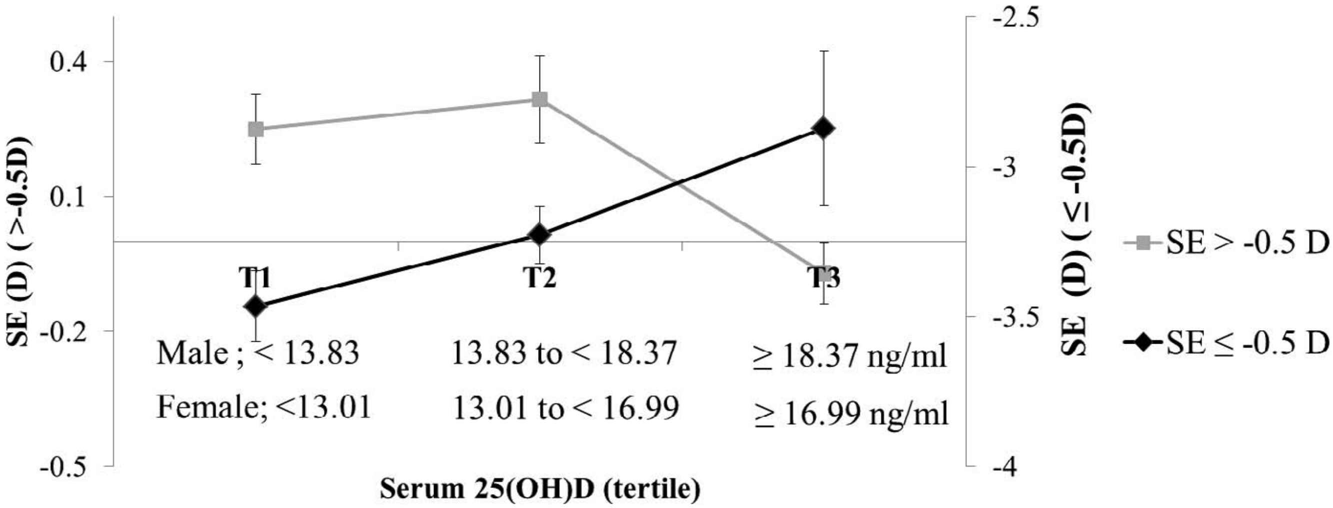

Figure 3. The changes of serum 25(OH)D concentration according to the SE in the myopia group and the nonmyopia group. Spherical equivalent values in myopia subjects declined significantly as serum 25(OH)D level decreased across the tertiles ($P = 0.020$). Tertile (T) cutoff values of 25(OH)D (ng/mL) were T1 less than 13.83, T2 13.83 to less than 18.37, T3 greater than or equal to 18.37 for male adolescents, and T1 less than 13.01, T2 13.01 to less than 16.99, T3 greater than or equal to 16.99 for female adolescents.

Significant protective association between increasing time outdoors and myopia has been reported.[9–11] However, the mechanisms how time outdoors might affect refractive error development is not entirely understood. The hypothesis for the association, includes the increased retinal dopamine in response to brighter light intensity in outdoors,[8] (as shown in animal model in which the increased dopamine release was shown to suppress axial elongation[29]), and the increased depth of focus in response to brighter light intensity and the low accommodative demand for distance vision.[30] As suggested by Mutti et al.,[16,28] it may also be related with the cutaneous synthesis of vitamin D, a product of sunlight.

Vitamin D is an essential component for intestinal absorption of Ca, playing an important role in bone growth and mineral and Ca homeostasis.[21] The 25(OH)D concentration is the most commonly used indicator of vitamin D status.[15] Childhood to adolescence is a critical period for bone accretion and growth; therefore, low–vitamin D status in this period is associated with numerous negative skeletal or other systemic consequences.[18] Also, there is increasing evidence that serum 25(OH)D level is relevant to several chronic diseases, including metabolic syndrome, cardiovascular, autoimmune and infectious diseases, and cancer.[1,18] Recent data for KNHANES 2008 showed that vitamin D insufficiency was highly prevalent in Korean adolescents, particularly those in higher school grades.[19] Adolescents are susceptible to myopia incidence and progression. In the Australian Myopia Progression Study, the annual incidence of myopia was 2.2% and 4.1% in those aged 12 and 17 years, respectively.[31] Considering of the epidemiologic evidence that time spent in outdoors has a protecting effect on myopia and the genetic basis on the association of vitamin D and myopia,[9,16,32,33] vitamin D deficiency in adolescence period is presumed to affect the incidence or progression of myopia.

In this study, there was a positive relationship between serum 25(OH)D and refractive error after adjustment for age (Fig. 2). This relationship retained significance after adjustment for the dietary factors related to serum 25(OH)D (milk consumption and Ca intake) and other confounding factors such as area of residence and socioeconomic status, which were associated with myopia prevalence in previous studies (Table 2). This suggests that serum 25(OH)D may also play a direct role in myopia development. One possibility is that low serum 25(OH)D might result in myopia development, via impaired contraction and relaxation of the ciliary muscles, because vitamin D is associated with alteration of intracellular

Table 2. Multiple Linear Regression Analysis for the Association Between Serum 25(OH)D Concentration and Refractive Error (D) in Korean Adolescents ($n = 2038$)

	Model 1: Adjusted for Age and Sex			Model 2: Adjusted for Age, Sex, Area of Residence, Parental Income, Total Energy Intake, Milk Consumption, Daily Calcium Intake, and Smoking		
	Beta	95% CI	*P* Value	Beta	95% CI	*P* Value
Serum 25(OH)D concentration	0.03	0.00, 0.05	0.012	0.03	0.00, 0.06	0.047
Age	−0.09	−0.16, −0.03	0.035	−0.10	−0.17, −0.02	0.016
Sex	−0.07	−0.30, 0.16	0.121	0.10	−0.16, 0.36	0.451
Area of residence				−0.36	−0.70, −0.03	0.035
Low income				0.61	0.13, 1.09	0.012
Total energy intake				0.07	−0.08, 0.23	0.349
Milk consumption				−0.14	−0.43, 0.15	0.329
Daily calcium intake (≥DRI)				−0.37	−0.84, 0.09	0.115
Smoking experience				0.63	0.25, 1.00	0.001

Table 3. Multiple Logistic Regression Analysis for the Association Between Serum 25(OH)D Tertiles and High Myopia in Myopic Korean Adolescents ($n = 1633$)

	Model 1: Adjusted for Age and Sex			Model 2: Adjusted for Age, Sex, Area of Residence, Parental Income, Total Energy Intake, Milk Consumption, Daily Calcium Intake, and Smoking		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Serum 25(OH)D T3 vs. T1	0.57	0.37, 0.89	0.016	0.55	0.34, 0.90	0.017
Serum 25(OH)D T2 vs. T1	0.82	0.53, 1.27		0.69	0.41, 1.14	
Age	1.20	1.08, 1.33	<0.001	1.23	1.09, 1.39	<0.001
Sex	1.02	0.70, 1.48	0.490	0.88	0.58, 1.33	0.542
Area of residence				0.84	0.51, 1.39	0.500
Low income				0.69	0.31, 1.53	0.363
Total energy intake				0.72	0.53, 0.97	0.032
Milk consumption				1.15	0.76, 1.74	0.509
Daily calcium intake (≥DRI)				0.62	0.27, 1.38	0.241
Smoking experience				0.48	0.24, 0.95	0.036

Ca level.[33–35]Another possibility is that Ca deficiency secondary to vitamin D deficiency causes head deformity, which may be include deformation of the orbits, leading to myopia of prematurity, as shown in the study of Carroll et al.[36] They reported that the extra-enteral Ca supplementation did not change refractive status in extremely low birth weight infants, because head shape was not changed in Ca supplementation group.[36]

In this study, the association between serum 25(OH)D and refractive error was particularly evident in the populations with high myopia (Table 3). High myopia is associated with reduced scleral collagen accumulation, scleral thinning, and loss of scleral tissue.[37] In myopic ocular growth, it is known that the retinoscleral signal pathway as well as IOP play a role.[37] Among several known local growth factors, retinoic acid is known to serve as a bidirectional factor in the retinoscleral signal, regulating eye growth.[38–40] Retinoic acid and VDR form heterodimers, which participate in signaling and cell-cycle regulation. Vitamin D is known to initiates the formation of the VDR/retinoic acid heterodimer.[41] Therefore, the low-serum vitamin D status is thought to affect pathological scleral growth, possibly via retinoic acid. The proteomic and genetic association between VDR and high myopia shown in previous studies may support this hypothesis.[32,33] Despite several line of genetic evidences, however, the interplay of environmental and genetic polymorphisms at multiple loci needs to be considered, as myopia is a multifactorial disease.

Our study has some limitations. First, the refractive status was not checked under cycloplegic conditions and the range of hyperopic refractive errors could be compressed in the regression analysis due to involuntary accommodation. However, we tried to reduce the potential misclassification of a myopia diagnosis using the subject's wearing of correction glasses. The study may also be confounded by a lack of data on relevant variables such as information on total time outdoors, parental myopic status, season of measurement, and sunlight exposure. In this study, measurement of sunlight exposure was substituted by regular physical activity. Regular physical activity is known to affect the level of serum vitamin D in a previous study.[20] Further supporting variables related to outcomes of vitamin D such as serum parathyroid hormone levels or bone parameters were not measured. These limitations should be addressed in future studies.

Myopia is one of the most common causes of visual impairment worldwide, and the high cost associated with its correction significantly contributes to public health and economic concerns. The apparent association of low serum 25(OH)D concentration with myopia, particularly with high myopia, suggests that more attention should be paid to efforts such as increasing vitamin D supplementation, as well as increasing the engagement of children in outdoor activity to prevent myopia. Basic interventional research on relevant mechanisms of low serum 25(OH)D concentration on scleral growth is needed.

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