

RESEARCH ARTICLE

Low Serum 25-Hydroxyvitamin D Levels Are Associated with Dry Eye Syndrome

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Abstract

Background

Dry eye syndrome (DES) is a common tear film and ocular surface disease that results in discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. Systemic diseases associated with DES include diabetes mellitus, rheumatoid arthritis, depression, anxiety, thyroid disease, allergic diseases, irritable bowel syndrome, chronic pain syndrome, and hyperlipidemia. Interestingly, it has been found that most of these are associated with low levels of serum 25-hydroxyvitamin D (25(OH)D) or inadequate sunlight exposure.

Methods

In this cross-sectional data analysis, noninstitutionalized adults aged ≥ 19 years (N = 17,542) who participated in Korean National Health and Nutrition Examination Survey 2010–2012 were included. Information regarding duration of sunlight exposure was collected from the survey participants. Serum 25(OH)D and zinc levels were measured. The confounding variables were age, gender, sunlight exposure time, region of residence, obesity, serum 25(OH)D level, diabetes mellitus, rheumatoid arthritis, depression, thyroid disorder, atopic dermatitis, history of ocular surgery, regular exercise, and walking exercise.

Results

Mean serum 25(OH)D levels of subjects with and without DES were 16.90 ± 6.0 and 17.52 ± 6.07 ($p < 0.001$). Inadequate sunlight exposure time (odds ratio [OR], 1.554; 95% confidence interval [CI], 1.307–1.848), urban residence (OR, 1.669; 95% CI, 1.456–1.913), indoor occupation (OR, 1.578; 95% CI, 1.389–1.814), and low serum 25(OH)D level (OR, 1.158; 95% CI, 1.026–1.308) were the risk factors for DES. After adjusting for age, sex, obesity, diabetes mellitus, rheumatoid arthritis, depression, thyroid disorder, atopic dermatitis, history of ocular surgery, regular exercise, and occupation, low serum 25(OH)D level (OR,

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1.178; 95% CI, 1.010–1.372) and deficient sunlight exposure time (OR, 1.383; 95% CI, 1.094–1.749) were the risk factors for diagnosed DES.

Conclusion

Low serum 25(OH)D levels and inadequate sunlight exposure are associated with DES in Korean adults. These results suggest that sufficient sunlight exposure or vitamin D supplementation may be useful in DES treatment.

Introduction

Dry eye syndrome (DES) is a common tear film and ocular surface disease that results in discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface [1]. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface [1]. DES significantly affects the quality of life owing to symptoms of pain and irritation [2]. Inflammation is recognized to play an important role in the pathogenesis of DES [3]. Chronic inflammation stimulated by the activation of innate immune components in ocular surface cells as well as increased tear osmolarity has been involved in DES [4]. DES is a multifactorial disease associated with systemic as well as local disease [1]. Blepharitis, meibomian gland dysfunction, eyelid deformity, and conjunctivochalasis are known risk factors for DES. Systemic diseases associated with DES include diabetes mellitus, rheumatoid arthritis, depression, anxiety, thyroid disease, allergic diseases, irritable bowel syndrome, chronic pain syndrome, and hyperlipidemia [5–9]. Interestingly, it has been found that most of these are associated with low levels of serum 25-hydroxyvitamin D (25(OH)D) or inadequate sunlight exposure [10–17].

Vitamin D is produced during exposure to sunlight, and is known to regulate calcium and phosphate homeostasis [10]. However, vitamin D receptor has been discovered in most tissues and cells in human body, including corneal epithelial cells [18], salivary glands [19,20], mammary glands [10], sebaceous glands [21], and immune cells [10]. Vitamin D has been suggested to play an essential role in these organs. Low serum vitamin D levels have been reported to be associated with obesity, diabetes mellitus, inflammatory bowel disease, atopic dermatitis, depression and autoimmune diseases [11–17]. Vitamin D exerts modulating effects on the immune response of both the innate and adaptive immune systems [22]. Furthermore, the active metabolite of 25(OH)D, 1, 25-dihydroxyvitamin D, has been found to regulate cytokine production and cell proliferation [23]. Serum 25(OH)D levels have been reported to be the most accurate way to measure vitamin D status in the body. In the kidney, 25-hydroxy vitamin D changes into an active form of the vitamin D, 1, 25-dihydroxyvitamin D [17]. A few studies have reported the association between serum vitamin D levels and dry eye syndrome has been reported [24,25]. However, those studies have a limitation of small sample size. The association of serum vitamin D levels and sunlight exposure time on DES have not been sufficiently evaluated.

In this study, we used the Korean National Health and Nutrition Examination Survey (KNHANES) to investigate the association of vitamin D deficiency and sunlight exposure time on DES in large population.

Methods

Study population

The Korean National Health and Nutrition Examination Survey (KNHANES) is a series of cross-sectional surveys of nationally representative samples of the civilian Korean population aged 1 year and older that are conducted annually to assess the health and nutrition status of

the South Korean population. To obtain representative samples, the KNHANES uses a stratified, multistage, cluster probability sampling design according to geographical area, age, and gender. More details regarding the sampling method are provided elsewhere [11]. The main components of the overall KNHANES survey are a health interview, health examination survey, and nutrition survey. For the health interview survey, a trained interviewer asked questions directly to individuals aged ≥ 19 years. This study included 17,542 adults (7,434 men and 10,108 women) aged ≥ 19 years who met the eligibility criteria and who completed a questionnaire regarding independent risk factors and underwent slit-lamp examinations.

Ethics statement

The KNHANES was approved by the Korean Centers for Disease Control and Prevention Institutional Review Board, and all participants provided written informed consent. This study adhered to the tenets of the Declaration of Helsinki.

Data collection and diagnostic criteria

For accurate data collection, participants were asked whether they have had DES symptoms (self-reported) and whether they have been previously diagnosed with DES. Subjects were asked the following question: “Until now, have you ever had dry eye symptoms before; for example, dryness of the eye or a sense of irritation?” (symptoms of DES; sxDES) Then, the subjects were asked: “To date, have you ever before been diagnosed by a physician as having a dry eye (either eye)?; emphasis was placed on the phrase “by a physician” [26]. The possible responses to the question about a previous diagnosis were “No” or “Yes” (diagnosed DES; dgDES). Data collected by the 2010–2012 KNHANES were analyzed in the present study.

Variables

The population was divided according to residential area: rural or urban. Occupation was classified on the basis of Korean Standard Classification of Occupations as follows: group 1 (managers, professionals, and related workers); group 2 (clerks); group 3 (service and sales workers); group 4 (skilled agricultural, forestry, and fishery workers); group 5 (craft, equipment, and machine operating and assembling workers); group 6 (elementary workers); and group 7 (housewives, students, and the unemployed). In this study, groups 1, 2, 3, and 7 were merged into a single group (indoor occupation) and groups 4, 5, and 6 (outdoor occupation) also were merged, because the latter groups were reported previously to have significantly higher serum 25(OH)D levels than the former groups [11]. Obesity was defined as body mass index over 30 kg/m^2 . Diabetes mellitus was defined as fasting plasma glucose $\geq 125 \text{ mg/dL}$ and impaired fasting glucose as fasting plasma glucose $\geq 110 \text{ mg/dL}$ [27]. Participants were asked whether they had had rheumatoid arthritis, depression, thyroid disease, atopic dermatitis, or ocular surgery. Participants who performed moderate physical activity for more than 30 min per day on more than 5 days per week and/or strenuous physical activity for more than 20 min per day on more than 3 days per week were assigned to the regular exercise group. Regular walking was defined as walking for more than 30 min per day on more than 5 days per week, as described previously [12,14]. Data on current sunlight exposure time was obtained by selecting a single answer to the following two questions: exposure time of under 5 h, or over 5 h a day.

Measurement of serum 25-hydroxyvitamin D and zinc levels

Blood samples were collected from the antecubital veins, refrigerated immediately, transported to the central testing facility in cold storage, and analyzed within 24 h of sampling. Serum 25

(OH)D levels were measured as described previously [13] and categorized as adequate (>20 ng/mL), inadequate (range, 12 to <20 ng/mL), or deficient (<12 ng/mL), according to the guidelines set by the Food and Nutrition Board of the Institute of Medicine [28].

Statistical analyses

Statistical analyses were performed by using the SPSS Version 18.0 (SPSS Inc., IBM Software, Portsmouth, UK), and 2-sided *P*-values of less than .05 were considered statistically significant. To produce unbiased national estimates representing the general Korean population, we used KNHANES sample weights accounting for the complex sampling design to each participant [29].

Chi-square test was used for comparison of discrete variables between groups. Student's *t*-test for independent samples was used for comparison of the differences between groups. The percentage differences were calculated as the absolute value of the change in value, divided by the average of the 2 numbers, all multiplied by 100. To estimate odds ratios (ORs) of dgDES and sxDES according to serum vitamin D levels, we conducted the logistic regression analyses by using the generalized linear model for a complex survey design. The ORs and 95% confidence intervals (CIs) were calculated in the following ways: no adjustment for potential confounders; confounder adjustment for age and gender.

Results

General characteristics

Characteristics of the study population are shown in Table 1. Mean age of the complete study population was 50.88 ± 16.67 years. The overall prevalence of dgDES was 10.39% (95% CI, 9.93% to 10.84%), and the prevalence of sxDES in the past 3 months was 17.79% (95% CI, 17.21% to 18.36%). Mean age among participants with dgDES (51.64 ± 16.28 years) was higher compared with non-dgDES (50.79 ± 16.71 years; $p = 0.004$, independent *t*-test). Pearson χ^2 test showed significant differences between age, gender, residential region, occupation, rheumatoid arthritis, depression, thyroid disease, history of ocular surgery, regular exercise, serum 25(OH)D levels, sunlight exposure time, and dgDES. In contrast to the factors that were associated with dgDES, those that were associated with sxDES were age, gender, residential region, occupation, depression, thyroid disease, history of ocular surgery, regular exercise, walking exercise, serum zinc levels, serum 25(OH)D levels, and sunlight exposure time (Table 1).

In a binary logistic regression analysis, the risk factors for dgDES included older age (odds ratio [OR], 1.179; 95% confidence interval [CI], 1.070–1.300), female gender (OR, 2.772; 95% CI, 2.473–3.108), rheumatoid arthritis (OR, 1.642; CI, 1.264–2.134), depression (OR, 1.637; 95% CI, 1.450–1.849), thyroid disease (OR, 2.244; 95% CI, 1.853–2.718), history of ocular surgery (OR, 1.284; 95% CI, 1.166–1.414), urban residence (OR, 1.583; 95% CI, 1.385–1.810), indoor occupation (OR, 1.841; 95% CI, 1.618–2.096), low serum 25(OH)D levels (<20 ng/mL; OR, 1.280; 95% CI, 1.139–1.439), and inadequate sunlight exposure time (OR, 1.696; 95% CI, 1.433–2.008). Regular exercise (OR, 0.823; 95% CI, 0.681–0.994) was a protective factor for dgDES. The risk factors for sxDES included older age (OR, 1.154; 95% CI, 1.066–1.249), female gender (OR, 2.221; 95% CI, 2.036–2.422), depression (OR, 1.662; 95% CI, 1.503–1.839), thyroid disease (OR, 1.818; 95% CI, 1.530–2.161), history of ocular surgery (OR, 1.099; 95% CI, 1.035–1.166), urban residence (OR, 1.197; 95% CI, 1.083–1.323), indoor occupation (OR, 1.433; 95% CI, 1.300–1.580), serum 25(OH)D levels (<12 ng/mL; OR, 1.271; 95% CI, 1.126–1.434), <110 $\mu\text{g/dL}$ zinc levels (OR, 1.443; 95% CI, 1.127–1.848), and inadequate sunlight exposure time (OR, 1.696; 95% CI, 1.433–2.008). Regular exercise (OR, 0.828; 95% CI, 0.712–0.963) and walking exercise (OR, 0.919; 95% CI, 0.846–0.999) were the protective factors for sxDES.

Table 1. General characteristics of dry eye syndrome.

	Diagnosed DES (dgDES)				Symptoms of DES (sxDES)			
	Non-dgDES	dgDES	%difference	p-value	Non-sxDES	sxDES	%difference	p-value
Total								
N (%)	15720 (89.61%)	1822 (10.39%)			13948 (82.21%)	3018 (17.79%)		
Age (y)				<0.001*				<0.001*
<50	3453 (92.62%)	275 (7.38%)			6890 (83.28%)	1383 (16.72%)		
≥50	12267 (88.80%)	1547 (11.20%)	41.12		7058 (81.19%)	1635 (18.81%)	11.76	
Gender				<0.001*				<0.001*
Male	7023 (94.47%)	411 (5.53%)			6343 (88.50%)	824 (11.50%)		
Female	8697 (86.04%)	1411 (13.96%)	86.51		7605 (77.61%)	2194 (22.39%)	64.27	
Obesity				0.430				0.058
Non-obese	7702 (89.88%)	869 (10.12%)			6868 (82.83%)	1424 (17.17%)		
Obese	3594 (89.40%)	426 (10.60%)	4.63		3160 (81.42%)	721 (18.58%)	7.89	
Diabetes mellitus				0.713				0.927
Non-DM	10078 (89.57%)	1174 (10.43%)			8935 (82.21%)	1933 (17.79%)		
IFG	2681 (89.70%)	308 (10.30%)	1.25		2381 (82.10%)	519 (17.90%)	0.62	
DM	1486 (90.22%)	161 (9.78%)	6.43		1316 (82.56%)	278 (17.44%)	1.99	
Rheumatoid arthritis				<0.001*				0.051
Non-RA	14909 (89.75%)	1702 (10.25%)			13218 (82.26%)	2851 (17.74%)		
RA	368 (84.21%)	69 (15.79%)	42.55		330 (78.57%)	90 (21.43%)	18.84	
Depression				<0.001*				<0.001*
Non-depression	13068 (90.40%)	1387 (9.60%)			11659 (83.42%)	2317 (16.58%)		
Depression	2210 (85.20%)	384 (14.80%)	42.62		1889 (75.17%)	624 (24.83%)	39.85	
Thyroid disorder				<0.001*				<0.001*
Non-thyroid disorder	14710 (90.02%)	1630 (9.98%)			13054 (82.59%)	2752 (17.41%)		
Thyroid disorder	567 (80.08%)	141 (19.92%)	66.49		493 (72.29%)	189 (27.71%)	45.66	
History of ocular surgery				<0.001*				<0.001*
No	13435 (91.02%)	1326 (8.98%)			11999 (84.00%)	2285 (16.00%)		
Yes	2130 (81.86%)	472 (18.14%)	67.55		1831 (72.72%)	687 (27.28%)	52.12	
Atopic dermatitis				0.634				0.187
Non-AD	14590 (89.64%)	1687 (10.36%)			12944 (82.25%)	2793 (17.75%)		
AD	688 (89.12%)	84 (10.88%)	4.90		604 (80.32%)	148 (19.68%)	10.31	
Region of residence				<0.001*				<0.001*
Urban	12267 (88.80%)	1547 (11.20%)			10933 (81.67%)	2453 (18.33%)		
Rural	3453 (92.62%)	275 (7.38%)	41.12		3015 (84.22%)	565 (15.78%)	14.95	
Occupation				<0.001*				<0.001*
Indoor	11091 (88.30%)	1470 (11.70%)			9821 (80.86%)	2325 (19.14%)		
Outdoor	4128 (93.29%)	297 (6.71%)	54.21		3676 (85.83%)	607 (14.17%)	29.84	

(Continued)

Table 1. (Continued)

	Diagnosed DES (dgDES)				Symptoms of DES (sxDES)			
	Non-dgDES	dgDES	%difference	p-value	Non-sxDES	sxDES	%difference	p-value
Sunlight exposure time (h)				<0.001*				<0.001*
Sufficient (≥ 5)	2194 (93.24%)	159 (6.76%)			1906 (84.34%)	354 (15.66%)		
Inadequate (2–5)	3707 (90.68%)	381 (9.32%)	31.84		3292 (83.32%)	659 (16.68%)	6.31	
Deficient (< 2)	9790 (88.45%)	1278 (11.55%)	52.32		8722 (81.35%)	2000 (18.65%)	17.43	
Regular exercise				0.043*				0.014*
No	13929 (89.44%)	1644 (10.56%)			12336 (81.93%)	2721 (18.07%)		
Yes	1318 (91.15%)	128 (8.85%)	17.62		1182 (84.55%)	216 (15.45%)	15.63	
Walking exercise				0.062				0.048*
No	9431 (89.24%)	1137 (10.76%)			8340 (81.68%)	1871 (18.32%)		
Yes	5800 (90.15%)	634 (9.85%)	8.83		5164 (82.90%)	1065 (17.10%)	6.89	
Serum zinc level (µg/dL)				0.091				0.004*
>110	742 (45.00%)	907 (55.00%)			624 (79.29%)	163 (20.71%)		
<110	89 (51.74%)	83 (48.26%)	13.05		801 (84.67%)	145 (15.33%)	29.86	
Serum 25(OH)D level (ng/mL)				<0.001*				0.001*
Adequate (≥20)	4390 (91.29%)	419 (8.71%)			3866 (83.68%)	754 (16.32%)		
Inadequate (12–20)	7892 (89.38%)	938 (10.62%)	19.76		7071 (82.35%)	1516 (17.65%)	7.83	
Deficient (<12)	2601 (60.39%)	1706 (39.61%)	127.89		2271 (80.13%)	563 (19.87%)	19.62	

*statistically significant by chi-square test

DES = dry eye syndrome; DM = diabetes mellitus; IFG = impaired fasting glucose; RA = rheumatoid arthritis; AD = atopic dermatitis

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Differences in mean serum 25-hydroxyvitamin D and zinc levels based on the presence of DES

From this adult Korean population, we determined whether serum levels of 25(OH)D or zinc correlated with dgDES or sxDES by comparing the estimated mean values. Without adjusting for potential confounders, the mean 25(OH)D levels were significantly lower in participants with dgDES or sxDES ($p < 0.001$ for both, independent t -test; Table 2). The mean serum zinc level was not different in participants with dgDES, but it was lower in participants with sxDES ($p = 0.001$, Table 2).

Serum 25(OH)D levels were lower in participants with the following characteristics: younger age, female gender, non-diabetes mellitus, rheumatoid arthritis, no history of ocular surgery, atopic dermatitis, urban residence, indoor occupation, low serum zinc levels, or inadequate sunlight exposure time ($p < 0.001$ for all except for rheumatoid arthritis, $p = 0.041$ for rheumatoid arthritis, independent t -test; Table 3) and higher in participants with regular exercise or walking exercise ($p < 0.001$ for both; Table 3).

Factors associated with developing DES

Table 4 shows the binary logistic regression analysis between dgDES and sxDES and potential risk factors adjusted for age and gender. The analysis showed that dgDES was associated with

Table 2. Serum 25(OH)D levels and zinc levels between groups.

	Diagnosed DES (dgDES)			Symptoms of DES (sxDES)		
	Non-dgDES	dgDES	p-value	Non-sxDES	sxDES	p-value
Serum 25(OH)D level (ng/mL)	17.52 ± 6.07	16.90 ± 6.08	<0.001*	17.51 ± 6.03	17.12 ± 6.13	0.001*
Serum zinc levels (µg/dL)	136.05 ± 29.58	131.80 ± 25.79	0.070	137.09 ± 29.45	131.20 ± 28.63	0.001*

*statistically significant by independent t-test

25-hydroxyvitamin D = 25(OH)D; DES = dry eye syndrome

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urban residence (OR, 1.669; 95% CI, 1.456–1.913), indoor occupation (OR, 1.587; 95% CI, 1.389–1.815), depression (OR, 1.059; 95% CI, 1.008–1.113), history of ocular surgery (OR, 1.203; 95% CI, 1.103–1.312), low serum 25(OH)D level (OR, 1.158; 95% CI, 1.026–1.308), and inadequate sunlight exposure time (OR, 1.554; 1.307–1.848). Further, it showed that sxDES was associated with urban residence (OR, 1.243; 95% CI, 1.122–1.377), indoor occupation (OR, 1.264; 95% CI, 1.143–1.399), obesity (OR, 1.115; 95% CI, 1.008–1.232), depression (OR, 1.075; 95% CI, 1.032–1.120), thyroid disease (OR, 1.046; 95% CI, 1.001–1.094), history of ocular surgery (OR, 1.070; 95% CI, 1.011–1.131), and regular exercise (OR, 0.843; 95% CI, 0.724–0.982).

After adjusting for age, sex, obesity, diabetes mellitus, rheumatoid arthritis, depression, thyroid disorder, atopic dermatitis, history of ocular surgery, regular exercise, and occupation, low serum 25(OH)D levels were the risk factors for dgDES, but not for sxDES (OR, 1.105; 95% CI, 1.007–1.213). Inadequate (OR, 1.178; 95% CI, 1.010–1.372) and deficient serum 25(OH)D level (OR, 1.216; 95% CI, 1.007–1.469) were the risk factors for dgDES (Table 5).

Discussion

DES is a common ocular disease in the general population and affects vision-related quality of life [1,30]. DES has been associated with various factors [7,30]. However, the associations between serum 25(OH)D levels and DES or between sunlight exposure time and DES have not been investigated.

In this study, we found that older age, female gender, rheumatoid arthritis, depression, thyroid disorder, history of ocular surgery, urban residence, indoor occupation, inadequate sunlight exposure, and low serum 25(OH)D level were the risk factor for dgDES. Older age and female gender are relatively well-known risk factors [6,7]. Aging, which is an important risk factor for DES, has been reported to be associated with lacrimal dysfunction [31]. Low estrogen levels after menopause in women have been described as being a major contributing factor for DES [32]. Androgen, estrogen, and progesterone receptor mRNAs have been identified in the eye [32]. Sex hormones are known to influence the immune system, and estrogen itself may modulate a cascade of inflammatory events that underlie DES [33]. Rheumatoid arthritis, depression, thyroid disorder, and history of ocular surgery are the well-known risk factors for DES [5–9,26]. DES is a common ocular manifestation in rheumatoid arthritis patients even though the severity of DES is independent of rheumatoid arthritis activity [34]. The association of DES and Graves' ophthalmopathy have been described to suggest the mechanical impairment of orbital muscles and immune-mediated lacrimal gland dysfunction [35]. Depression is not only a risk factor for DES but anticholinergic effects of anti-depressant also can induce DES [36]. Ocular surgery induces the changes in corneal innervation which play an essential role in the pathogenesis of dry eye syndrome [37].

Urban residence and indoor occupation were the risk factors for dgDES and sxDES. In previous studies, urban dwellers and subjects with indoor occupations were reported to be factors

Table 3. Serum 25(OH)D level (ng/mL).

	Serum 25(OH)D level (ng/mL)	p-value
Age (y)		<0.001*
<50	16.25 ± 5.26	
>50	18.70 ± 6.46	
Gender		<0.001*
Male	18.45 ± 5.97	
Female	16.49 ± 5.80	
Obesity		0.660
Non-obese	17.37 ± 5.95	
Obese	17.32 ± 6.02	
Diabetes mellitus		<0.001*
Non-DM	17.20 ± 5.94	
IFG	18.19 ± 6.09	
DM	18.25 ± 6.65	
Rheumatoid arthritis		0.041*
Non-RA	17.46 ± 6.06	
RA	18.15 ± 6.72	
Depression		0.718
Non-depression	17.49 ± 6.01	
Depression	17.44 ± 6.18	
Thyroid disorder		0.405
Non-thyroid disorder	17.47 ± 6.06	
Thyroid disorder	17.67 ± 6.31	
History of ocular surgery		<0.001*
No	17.39 ± 5.99	
Yes	17.91 ± 6.58	
Atopic dermatitis		<0.001*
Non-AD	17.52 ± 6.09	
AD	16.69 ± 5.58	
Region of residence		<0.001*
Rural	19.16 ± 6.47	
Urban	16.91 ± 5.74	
Occupation		<0.001*
Groups 4, 5 and 6 (outdoor)	19.22 ± 6.48	
Groups 1,2,3, and 7 (indoor)	16.73 ± 5.73	
Sunlight exposure time (h)		<0.001*
≥5	20.16 ± 6.55	
2–5	17.83 ± 6.12	
<2	16.77 ± 5.78	
Regular exercise		<0.001*
No	17.31 ± 5.99	
Yes	18.66 ± 6.46	
Walking exercise		<0.001*
No	17.25 ± 5.60	
Yes	17.71 ± 6.16	
Serum zinc levels (µg/dL)		<0.001*
≥110	18.61 ± 6.49	
<110	16.78 ± 5.81	

* statistically significant by independent t-test

DES = dry eye syndrome; DM = diabetes mellitus; IFG = impaired fasting glucose; RA = rheumatoid arthritis; AD = atopic dermatitis

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Table 4. Factors that affect the occurrence of dry eye syndrome after adjusting for age and gender.

	Diagnosed DES			Symptoms of DES		
	OR	95% CI	p-value	OR	95% CI	p-value
Region of residence						
Rural	1.0 (ref)			1.0 (ref)		
Urban	1.669	1.456–1.913	<0.001*	1.243	1.122–1.377	<0.001*
Occupation						
Outdoor	1.0 (ref)			1.0 (Ref)		
Indoor	1.587	1.389–1.815	<0.001*	1.264	1.143–1.399	<0.001*
Obesity						
Non-obese	1.0 (ref)			1.0 (ref)		
Obese	1.069	0.944–1.210	0.291	1.115	1.008–1.232	0.034*
Diabetes mellitus						
Non-DM	1.0 (ref)			1.0 (ref)		
IFG	1.067	0.929–1.224	0.359	1.075	0.962–1.202	0.200
DM	0.955	0.796–1.145	0.618	0.998	0.864–1.155	0.984
Rheumatoid arthritis						
Non-RA	1.0 (ref)			1.0 (ref)		
RA	1.026	0.969–1.085	0.380	1.025	0.978–1.074	0.299
Depression						
Non-depression	1.0 (ref)			1.0 (ref)		
Depression	1.059	1.008–1.113	0.024*	1.075	1.032–1.120	0.001*
Thyroid disorder						
Non-thyroid disorder	1.0 (ref)			1.0 (ref)		
Thyroid disorder	1.053	1.000–1.109	0.051	1.046	1.001–1.094	0.045*
History of ocular surgery						
No	1.0 (ref)			1.0 (ref)		
Yes	1.203	1.103–1.312	<0.001*	1.070	1.011–1.131	0.019*
Atopic dermatitis						
Non-AD	1.0 (ref)			1.0 (ref)		
AD	1.124	0.888–1.423	0.330	1.199	0.994–1.446	0.058
Sun exposure time (h)						
Sufficient (≥ 2)	1.0 (ref)			1.0 (ref)		
Inadequate (2–5)	1.389	1.143–1.690	0.001*	1.047	0.907–1.209	0.528
Deficient (<2)	1.630	1.367–1.944	<0.001*	1.119	0.984–1.271	0.085
Regular exercise						
No	1.0 (ref)			1.0 (ref)		
Yes	0.841	0.696–1.108	0.076	0.843	0.724–0.982	0.029*
Walking exercise						
No	1.0 (ref)			1.0 (ref)		
Yes	0.959	0.865–1.064	0.434	0.961	0.884–1.045	0.353
Serum 25(OH)D level (ng/mL)						
Adequate (≥ 20)	1.0 (ref)			1.0 (ref)		
Inadequate (12–20)	1.167	1.030–1.321	0.015*	1.036	0.939–1.143	0.483
Deficient (<12)	1.205	1.031–1.407	0.019*	1.113	0.982–1.262	0.094
Serum zinc level ($\mu\text{g/dL}$)						
≥ 110	1.0 (ref)			1.0 (ref)		

(Continued)

Table 4. (Continued)

	Diagnosed DES			Symptoms of DES		
	OR	95% CI	p-value	OR	95% CI	p-value
<110	0.926	0.671–1.278	0.638	0.798	0.620–1.029	0.081

*statistically significant by logistic regression analysis

DES = dry eye syndrome; OR = odds ratio; CI = Confidence interval; DM = diabetes mellitus; IFG = impaired fasting glucose; RA = rheumatoid arthritis; AD = atopic dermatitis

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associated with DES [8,38,39]. They have been described to be due to low indoor humidity [40], air pollution [9,41], and visual display terminal (VDT) syndrome, which is accompanied by lower blinking rates and increased tear evaporation [42]. However, the reason for the prevalence of DES in urban residency and among those with indoor occupations has not been understood thoroughly. We noticed that the participants with both urban residence and indoor occupations were exposed to sunlight inadequately. Thus, we evaluated the associations between sunlight exposure time and dgDES or sxDES. We found that inadequate sunlight exposure time (<5 h) was a risk factor for dgDES, but not for sxDES. It has been reported that sunlight exposure should be avoided, because it contributes to an increased risk of dry age-related macular degeneration, cataract, and pterygium [43]. However, sunlight exposure has been reported to prevent the development of myopia [44], depression [45,46], anxiety [16,47], diabetes [15], and autoimmune disease [48]. Sunlight exposure is by far the most important source of vitamin D [15,49]. The human skin has a large capacity for vitamin D production [49]. Vitamin D₃ is synthesized in the skin from 7-dehydrocholesterol under the influence of UV-B (wavelength, 290–315 nm) radiation and temperature [50]. In this study, serum 25(OH)D levels were lower in DES compared to non-DES. After adjusting for age and gender, inadequate serum 25(OH)D levels (<20 ng/mL) were a risk factor with dgDES. However, sxDES was associated only with deficient serum 25(OH)D levels (<12 ng/mL), not with inadequate levels (<20 ng/mL). Vitamin D receptor has been reported to exist in ocular barrier cells [18]. It has been suggested that vitamin D might have a role in immune regulation and barrier function in ocular barrier epithelial cells [18]. Vitamin D has been reported to enhance corneal

Table 5. Relationship of serum 25-hydroxyvitamin D level and dry eye syndrome.

	Diagnosed DES			Symptoms of DES		
	OR	95% CI	p-value	OR	95% CI	p-value
Sunlight exposure time (h)						
Sufficient (≥2)	1.0 (ref)			1.0 (ref)		
Inadequate (2–5)	1.142	0.882–1.479	0.314	0.978	0.809–1.182	0.815
Deficient (<2)	1.383	1.094–1.749	0.007*	1.050	0.885–1.246	0.575
Serum 25(OH)D level (ng/mL)						
Adequate (≥20)	1.0 (ref)			1.0 (ref)		
Inadequate (12–20)	1.178	1.010–1.372	0.036*	1.045	0.926–1.179	0.475
Deficient (<12)	1.216	1.007–1.469	0.043*	1.115	0.957–1.298	0.163

Adjusted by age, sex, obesity, diabetes mellitus, rheumatoid arthritis, depression, thyroid disorder, atopic dermatitis, history of ocular surgery, regular exercise, occupation and residence. 25-hydroxyvitamin D = 25(OH)D; DES = dry eye syndrome; OR = odds ratio; CI = Confidence interval

*statistically significant by logistic regression analysis

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epithelial barrier function [51] through regulating gap junctions [52] and tight junction [53]. Vitamin D exerts an immunomodulating effect on the immune system [14]. In mice, vitamin D has been shown to suppress ocular surface inflammation by inhibiting Langerhans cell migration into corneas [54], thus inhibiting corneal neovascularization [55]. Furthermore, salivary glands and their epithelial and myoepithelial cells are major vitamin D targets [19], and fluid and electrolyte secretion from the parotid gland is dependent on vitamin D directly [20]. Thus, lacrimal glands as well as corneal epithelial cells also may be affected by vitamin D. It has been reported that vitamin D deficiency is prevalent in patients with Sjogren's syndrome and that female patients with Sjogren's syndrome are at risk for vitamin D deficiency [56].

In this study, we evaluated the effect of exercise on DES. After adjusting for age and gender, regular and walking exercise did not affect dgDES. However, regular exercise was a protective factor for sxDES. Regular exercise has an acute effect on salivary hormone response [57]. Regular exercise may be helpful in reducing symptoms in patients with DES. Serum zinc levels, in this study, were lower in sxDES group compared to non-sxDES group. Zinc has a role in retinal metabolism and may be beneficial in macular degeneration [58]. Zinc ion-dependent B-cell epitope is associated with primary Sjogren's syndrome [59]. However, after adjusting for age and gender, serum zinc levels did not affect sxDES. The discrepancy between the sunlight exposure and serum 25(OH)D level has been reported [60]. Serum vitamin D status can be remained despite abundant sun exposure [60]. Vitamin D obtained from the diet or cutaneous synthesis is readily taken up by adipose tissue [61]. Bioavailability of vitamin D has been reported to be reduced in obesity [62]. Thus, obesity should be considered as a confounding factor for evaluation of the effect of vitamin D. After adjusting age, gender, diabetes mellitus, rheumatoid arthritis, depression, thyroid disorder, atopic dermatitis, history of ocular surgery, regular exercise, obesity, and occupation, deficient sunlight exposure and inadequate and deficient serum 25(OH)D levels were a risk factor for DES.

In conclusion, deficient sunlight exposure time and inadequate serum 25(OH)D levels are associated with DES in Korean adults. These results suggest that sufficient sunlight exposure and/or vitamin D supplementation may be helpful in treatment of DES.

Supporting Information

S1 Dataset. Dataset containing the KNHANES (2010–2012).
(XLS)

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Author Contributions

Conceived and designed the experiments: YJS SGP SHH. Performed the experiments: SY Y SHB YJS. Analyzed the data: SY Y SHB YJS WRW. Contributed reagents/materials/analysis tools: SHB YJS JYH. Wrote the paper: SY Y SHB YJS.

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