

# Dry Eye Evaluation in Saudi Patients with Vitamin D Deficiency

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## Abstract

**Purpose:** The aim of this study was to investigate tear film function and dry eye syndrome in Saudi patients with vitamin D deficiency.

**Design:** This study was a non-randomized, cross-sectional, observational, and quantitative study.

**Subjects and Methods:** This study included 75 patients with vitamin D deficiency (group 1), and 25 healthy subjects (group 2). All subjects completed ocular surface disease index (OSDI) questionnaire and underwent to a full ophthalmological examination. The dry eye was assessed in this order: tear break-up time (TBUT), corneal fluorescein staining scoring using the Oxford Schema, and anesthetized Schirmer test (Schirmer II). Measurement of serum 25-hydroxyvitamin D level was done using Enzyme Linked Immunosorbent Assay (ELISA) in the laboratory. All patients were recruited from College of Applied Medical Sciences, King Saud University, and Dwaak Medical Center, Riyadh, Saudi Arabia, by nonrandomized convenience sampling method from February to April 2017.

**Results:** The mean of superficial punctate staining, as measured by the Oxford scale was significantly higher ( $2.2 \pm 1.0$ ) in group 1 than in the control group ( $1.7 \pm 0.8$ ) ( $P = 0.02$ ). While there were no statistically significant differences regarding Schirmer II test values, TBUT measurements, and OSDI scores between the two groups ( $P > 0.05$ ).

**Conclusion:** To the best of our knowledge, this study is the first one conducted in Saudi Arabia. This study did not document significant correlation between dry eye syndrome and vitamin D deficiency in Saudi patients while other studies confirmed strong association. Future studies with a larger sample size and further investigations such as TearLab Osmometer are recommended to elucidate the role of vitamin D in dry eye pathogenesis.

**Keywords:** Dry Eye Syndrome; Vitamin D Deficiency; Schirmer Test; Tear Break-up Time (TBUT); Ocular Surface Disease Index (OSDI)

## Introduction

Dry eye syndrome is identified as a multifactorial disease of the tears and ocular surface. It is usually characterized by increased tear film osmolarity and ocular surface inflammation. It can lead to discomfort, tear film instability and blurred vision that may affect life quality [1].

Dry eye syndrome prevalence is estimated to be 7%-34% depending on the studied populations and the used investigations. The assessed prevalence in Al-Ahsa, Saudi Arabia, is 32.1% of the population [2].

Alsalem *et al.* [3] demonstrated that corneal epithelium, endothelium and retinal pigmentary epithelium have vitamin D receptors. Also, Yin *et al.* [4] documented that vitamin D plays an important role in enhancement of corneal epithelial barrier function. In addition, Sundar & Rahman [5] reported role of vitamin D in regulation of several genes integrated in inflammation, immunity, cellular proliferation, differentiation, and apoptosis. Furthermore, it has been found that Vitamin D mediates fluid and ion transport in salivary glands. Hence, it is suggested that tear secretion in the lacrimal glands may be controlled by vitamin D [6]. The incidence of Vitamin D deficiency in the Saudi Arabian population is around 60% [7].

Many studies demonstrated the relationship between dry eye syndrome and vitamin D deficiency [8,9]. Yildirim *et al.* [8] demonstrated significant correlation between vitamin D deficiency and TBUT, Schirmer II and OSDI. Therefore, they concluded that vitamin D deficiency may display a protective role of vitamin D in the development of dry eye, possibly by improving dry eye

parameters and decreasing ocular surface inflammation. Demirci *et al.* [9] demonstrated that vitamin D deficiency is associated with tear hyperosmolarity and tear film dysfunction. On the other hand, other studies didn't find significant relationship between dry eye and vitamin D deficiency. Such as, Galor *et al.* [10] did not find a strong association between vitamin D levels and most dry eye parameters. Also, Baldini *et al.* [11] found no significant difference in vitamin D levels between the patients with Sjögren's syndrome and controls. Therefore, the relationship between dry eye and vitamin D is still unclear. Up to our knowledge, this relationship is never investigated in Saudi Arabia. Demonstration of significant association between dry eye and vitamin D deficiency may be useful in management of dry eye syndrome as vitamin D supplementation may improve dry eye symptoms.

## Purpose

The aim of this study was to investigate tear film function and dry eye syndrome in Saudi patients with vitamin D deficiency.

## Subjects and Methods

### Design

This study was a nonrandomized, cross sectional, observational, and quantitative study. It got the approval of Research Ethics Committee of College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia. It adhered to the tenets of the Declaration of Helsinki. All the participants signed comprehensive consent after explanation of the possible consequences of the study prior to investigations.

The study included (only right eyes) of 75 patients (43 premenopausal women {57%} and 32 men {43%} [75 eyes]) with vitamin D deficiency (serum 25-hydroxyvitamin D levels of < 20 ng/mL) (group 1), and 25 eyes of 25 healthy individuals (16 premenopausal women {64%} and 9 men {36%} [25 eyes]) (serum 25-hydroxyvitamin D levels of  $\geq$  20 ng/mL) (group 2). The age range of group 1 was 20–45 years (mean: 24.4 $\pm$ 0.6 years), and the age range of group 2 was 20–45 years (mean: 24.4 $\pm$ 1.1 years). All patients were recruited from College of Applied Medical Sciences, King Saud University, and Dwaak Medical Center, Riyadh, Saudi Arabia, by nonrandomized convenience sampling method from February to April 2017. Exclusion criteria included presence of primary Sjögren syndrome or other systemic rheumatic disease history, vitamin B12 deficiency, vitamin A deficiency, a history of smoking, current or recent drug use that could affect the lacrimal functional unit, active ocular infection or allergy, ocular surface scarring, previous eye surgery, current contact lens use, use of any topical or systemic medication (including fatty acids such as omega-3, omega 6), and excessive nicotine and/or caffeine intake. In addition, postmenopausal and pregnant women were excluded from this study because previous studies have suggested that estrogen and progesterone receptors are present in lacrimal gland, cornea and meibomian gland [12].

Measurement of serum 25-hydroxyvitamin D level was done twice using Enzyme Linked Immuno-Sorbent Assay (ELISA) in the laboratory prior to participating in the study from February and April. The results were collected from the laboratory database. Vitamin D deficiency is defined as serum 25-hydroxyvitamin D levels of < 20 ng/mL [8].

All participants accomplished ocular surface disease index (OSDI) questionnaire which was used to evaluate the dry eye symptoms. Subjects were requested to answer questions concerning the symptoms of dry eye that they had practiced during a 1-week recall period; the OSDI questions comprised three dissimilar subscales: ocular symptoms, vision-related functions, and environmental irritating factors. Each response was recorded on a 4-point scale that extended from zero (demonstrating no problems) to four (demonstrating a significant problem). Answers to all questions were joined to generate a combination OSDI score that extended from 0 to 100, with higher OSDI scores signifying more severe symptoms and lower vision-related quality of life. Scores > 15 were recognized as indication of dry eye [8].

All subjects underwent a full ophthalmological examination in the same order, including visual acuity assessment, slit-lamp examination, and fundus examination. The examination was performed by one expert practitioner. Vitamin D status was masked to her. Testing of all subjects was performed in the same room at the same stable conditions. The dry eye examinations were performed in this order:

1. Tear Breakup Time which was used to test tear film stability. 2% Fluorescein solution was applied on the inferior palpebral conjunctiva. The participant was inquired to blink several times to distribute the fluorescein over the cornea and then stop. Then the tear film was examined with a cobalt blue light. Measurement of the period between a complete blink and the first appearance of a dry point on the cornea was then performed. An average of three measurements was registered. A tear break-up time < 10 sec was known as sign of dry eye [8].
2. Corneal fluorescein staining scoring using the Oxford Schema was performed. After application of the moistened fluorescein strip to the conjunctival sac, the entire cornea was scanned by slit-lamp evaluation with a yellow barrier filter and cobalt blue illumination. The staining was scored using the Oxford Scheme 6-point scale (from 0 through 5) [13].
3. Anesthetized Schirmer test (Schirmer II) was done for evaluating quantity of tears. It measures basic secretion and abolishes reflex secretion to a great extent. A 35 X 5 mm strip of Schirmer filter paper was introduced inside the lower eyelids of both eyes after topical anesthesia instillation. The strip was removed after 5 min. Moisture on the filter paper was then measured. Diagnosis of dry eye was documented if the measurement was < 6 mm [14]. Schirmer II is more objective and reliable than that without anesthesia in reflecting the status of dry eye [15].

## Statistical Analysis

Data were normally distributed and analyzed using statistical software (SPSS version 22.0). Descriptive statistics (mean and standard deviation [SD]) were used for assessing the demographics and clinical parameters. Independent samples t-test was used to compare the differences between the two studied groups. The level of the linear relation between the scales was evaluated by Pearson's correlation coefficient. A value of  $P < 0.05$  was considered statistically significant.

## Results

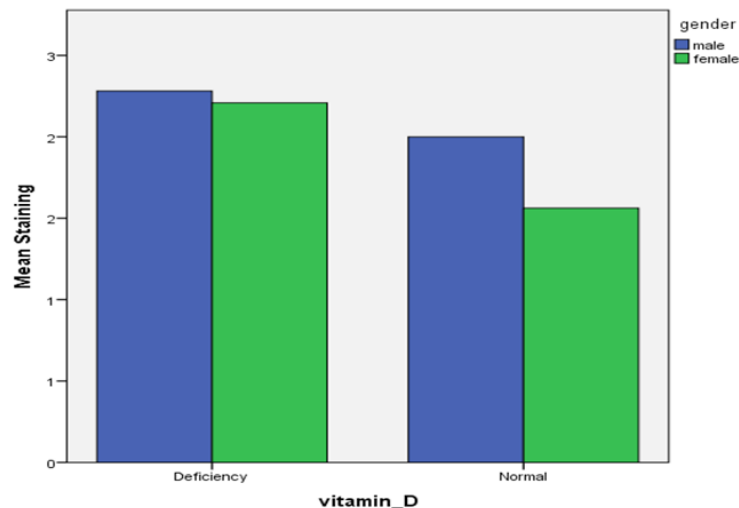
This study included 2 groups: 75 eyes of 75 patients with vitamin D deficiency (group 1) and 25 eyes of 25 healthy subjects (group 2) (control group). The mean age was  $24.4 \pm 0.6$  (20–45) years in group 1 and  $24.4 \pm 1.1$  (20–45) years in group 2. There were no significant differences between the groups with respect to age or sex ( $P = 1.0$  and  $P = 0.56$ , respectively). The mean of 25-hydroxyvitamin D (ng/mL) levels was lower  $10.0 \pm 4.4$  (2.8–18.6) in group 1 compared to  $26.8 \pm 6.9$  (20.3–46.0) in the control group.

The mean score of superficial punctate staining, as measured by the Oxford scale was significantly higher ( $2.2 \pm 1.0$ ) in group 1 than ( $1.7 \pm 0.8$ ) in group 2 ( $P = 0.02$ ). While there were no statistically significant differences regarding Schirmer II test values, TBUT measurements, and OSDI scores between the two groups ( $P > 0.05$ ). The mean of TBUT (sec) was ( $6.9 \pm 3.7$ ) in group 1 and ( $6.7 \pm 4.1$ ) in group 2 ( $P = 0.80$ ). The mean of Schirmer II test values (mm) was ( $23.1 \pm 7.7$ ) in group 1 and ( $24.3 \pm 7.0$ ) in group 2 ( $P = 0.49$ ). The mean of OSDI scores was ( $19.2 \pm 18.4$ ) in group 1 and ( $15.0 \pm 19.5$ ) in group 2 ( $P = 0.33$ ). Demographic and clinical data were demonstrated in (Table 1) (Figures 1,2,3 and 4). Regarding the frequencies of the subjects with dry eye in this study, there were no significant differences between the vitamin D deficiency group and control group (Table 2).

Parameter	Group 1 (vitamin D deficient) (n=75)	Group 2 (vitamin D sufficient) (n=25)	P value
Age (y) Mean $\pm$ SD Range	$24.4 \pm 0.6$ 20–45	$24.4 \pm 1.1$ 20–45	1.0
Vitamin D (ng/mL) Mean $\pm$ SD Range	$10.0 \pm 4.4$ 2.8–18.6	$26.8 \pm 6.9$ 20.3–46.0	<b>0.001*</b>
TBUT(sec) Mean $\pm$ SD Range	$6.9 \pm 3.7$ 1–18	$6.7 \pm 4.1$ 2–16	0.80
Staining Mean $\pm$ SD Range	$2.2 \pm 1.0$ 0–4	$1.7 \pm 0.8$ 0–3	<b>0.02*</b>
Schirmer II (mm) Mean $\pm$ SD Range	$23.1 \pm 7.7$ 6–35	$24.3 \pm 7.0$ 9–35	0.49
OSDI Mean $\pm$ SD Range	$19.2 \pm 18.4$ 0–65	$15.0 \pm 19.5$ 0–79	0.33

A value of  $P < 0.05$  was considered statistically significant (\*).

**Table 1:** Demographic and Clinical Data of the 2 Groups



**Figure 1:** Superficial Punctate Staining in 2 the Groups (Males and Females)

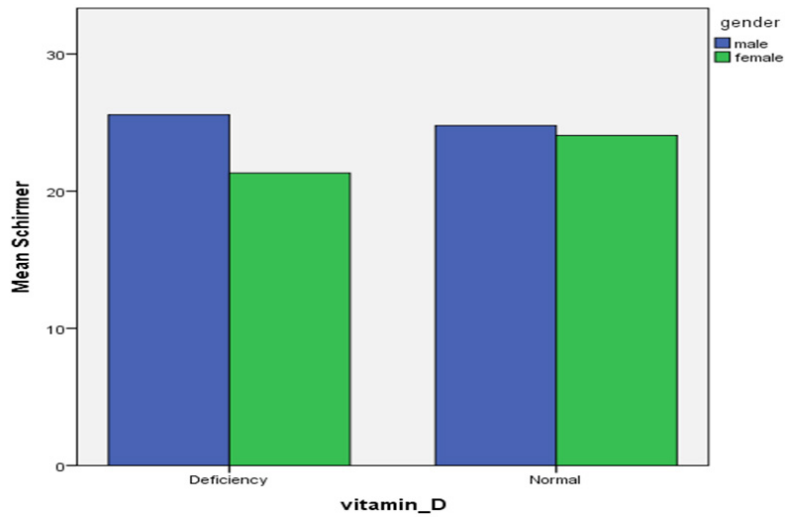


Figure 2: Schirmer II Test in the 2 Groups (Males and Females)

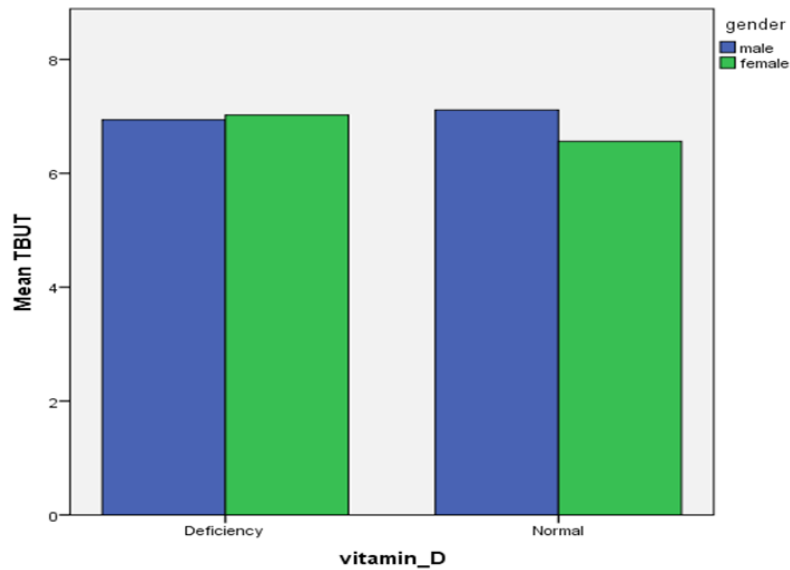


Figure 3: Tear Break up Time (TBUT) in the 2 Groups (Males and Females)

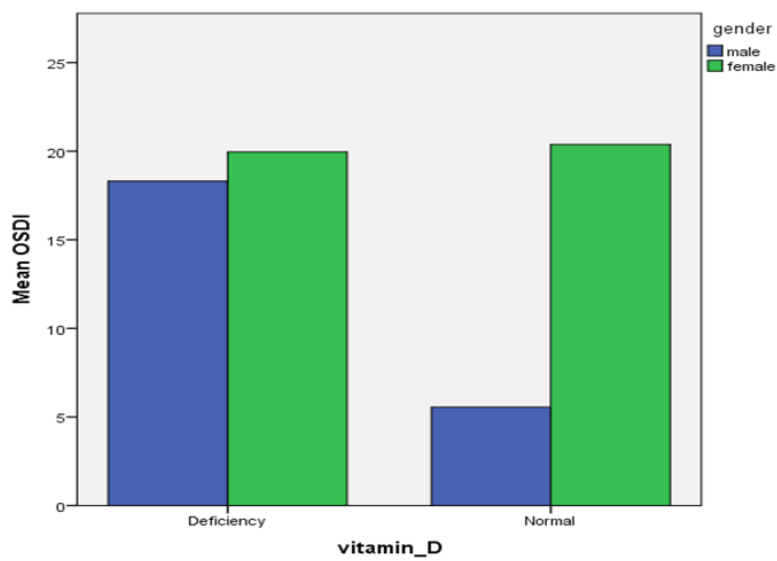


Figure 4: Ocular Surface Disease Index (OSDI) in the 2 Groups (Males and Females)

Parameter	Group 1 (vitamin D deficient) (n=75)	Group 2 (vitamin D sufficient) (n=25)	P value
Schirmer II ( $\leq 10$ mm)	3 (4%)	2 (8%)	0.49
TBUT (< 10 sec)	57 (76%)	18 (72%)	0.80
OSDI (> 15)	31 (41%)	8 (32%)	0.33

Table 2: Dry Eye Frequencies in the 2 Groups

Concerning assessment of dry eye parameters according to the gender in group 1: The mean of Schirmer II test values (mm) was significantly lower ( $21.3 \pm 7.5$ ) in females compared to ( $25.5 \pm 7.3$ ) in males ( $P = 0.01$ ). While no statistically significant differences regarding superficial punctate staining; TBUT measurements, and OSDI scores ( $P > 0.05$ ) were detected according to the gender. The mean of TBUT (sec) was lower ( $6.9 \pm 3.5$ ) in males compared to ( $7.0 \pm 4.0$ ) in females ( $P = 0.92$ ). The mean of superficial punctate staining, as measured by the Oxford scale was ( $2.3 \pm 0.9$ ) in males and ( $2.2 \pm 1.1$ ) in females ( $P = 0.77$ ). The mean of OSDI scores was lower ( $18.3 \pm 17.5$ ) in males compared to ( $19.9 \pm 19.2$ ) in females ( $P = 0.70$ ) (Table 3).

Parameter	Males (n=32)	Females (n=43)	P value
TBUT(sec) Mean $\pm$ SD Range	$6.9 \pm 3.5$ 1-14	$7.0 \pm 4.0$ 2-18	0.92
Staining Mean $\pm$ SD Range	$2.3 \pm 0.9$ 0-4	$2.2 \pm 1.1$ 0-4	0.77
Schirmer II (mm) Mean $\pm$ SD Range	$25.5 \pm 7.3$ 11-35	$21.3 \pm 7.5$ 6-35	<b>0.01*</b>
OSDI Mean $\pm$ SD Range	$18.3 \pm 17.5$ 0-62	$19.9 \pm 19.2$ 0-65	0.70

A value of  $P < 0.05$  was considered statistically significant (\*).

Table 3: Dry Eye Parameters in Group 1 according to the Gender

In this study, using Pearson's correlation liner regression analysis, serum 25-hydroxyvitamin D level in group 1 showed insignificant positive correlation with TBUT ( $r = 0.029$ ;  $P = 0.807$ ), and OSDI ( $r = 0.025$ ;  $P = 0.832$ ). Also, it showed insignificant negative correlation with Schirmer II test ( $r = -0.14$ ;  $P = 0.220$ ), and superficial punctate staining ( $r = -0.07$ ;  $P = 0.539$ ) (Table 4). On the other hand, the age of vitamin D deficiency subjects demonstrated significant positive correlation with superficial punctate staining ( $r = 0.25$ ;  $P = 0.03$ ) and insignificant negative correlation with TBUT ( $r = -0.024$ ;  $P = 0.836$ ). In addition, it showed insignificant positive correlation with Schirmer II test ( $r = 0.01$ ;  $P = 0.909$ ), and OSDI ( $r = 0.13$ ;  $P = 0.271$ ) (Table 5).

Parameter	r value	P value
TBUT	0.029	0.807
Staining	-0.07	0.539
Schirmer II	-0.14	0.220
OSDI	0.025	0.832

Table 4: Pearson's Correlation between dry eye parameters and serum 25-hydroxyvitamin D level in group 1

Parameter	r value	P value
TBUT	-0.024	0.836
Staining	0.25	0.03*
Schirmer II	-0.14	0.909
OSDI	0.13	0.271

A value of  $P < 0.05$  was considered statistically significant (\*).

Table 5: Pearson's Correlation between Dry Eye Parameters and the age in Group 1

## Discussion

This study investigated tear film function and dry eye syndrome in Saudi patients with vitamin D deficiency. Regarding assessment of dry eye parameters, the study showed that the mean of superficial punctate staining was significantly higher in group 1 than in the control group which matched with Demirci *et al.* [9] who evaluated 60 eyes of 30 patients with vitamin D deficiency (group 1), and

60 eyes of 30 healthy individuals (group 2) in Istanbul, Turkey. They demonstrated that tear osmolarity values, OSDI, and Oxford scale scores were significantly higher in group 1 compared with group 2. In addition, they found that Schirmer I test and TBUT results in group 1 were significantly lower compared with group 2. However, our study demonstrated no significant differences as regards TBUT, Schirmer II, which disagreed with Yildirim *et al.* [8] Demirci *et al.* [9] and Kurtul *et al.* [16] Yildirim *et al.* [8] investigated 50 premenopausal women with vitamin D deficiency and 48 controls in Turkey. They documented lower scores of Schirmer test, TBUT and higher scores of OSDI in patients with vitamin D deficiency compared to scores in the controls. Kurtul *et al.* study [16] included 34 patients with serum vitamin D deficiency and 21 controls in Ankara, Turkey. They showed that TBUT scores and Schirmer-1 results of the study group were significantly lower than the control group scores.

The current study found no significant differences related to dry eye symptoms using OSDI questionnaire which disagreed with Yildirim *et al.* [8], and Demirci *et al.* [9] In addition, no significant differences were detected between the 2 groups concerning dry eye frequencies which was not in agreement with Demirci *et al.* [9].

Concerning assessment of dry eye parameters according to the gender in vitamin D deficiency group: The mean of Schirmer II was significantly lower in females compared to males. While no statistically significant differences regarding superficial punctate staining; TBUT measurements, and OSDI scores were detected according to the gender. Up to our knowledge, no study investigated these procedures and comparing them according to the gender.

Using Pearson's Correlation Coefficient: This study demonstrated insignificant correlation with TBUT; Schirmer II, and OSDI which disagreed with Yildirim *et al.* [8] Furthermore, the age of vitamin D deficiency subjects in our study demonstrated insignificant correlation with TBUT, Schirmer II, and OSDI. Hong *et al.* [17] found insignificant correlation with TBUT only. However, Yildirim *et al.* [8] and Mathers *et al.* [18] demonstrated significant correlation with TBUT and Schirmer II. In addition, Yildirim *et al.* [8] found significant correlation with OSDI. Galor *et al.* [10] demonstrated no association between vitamin D levels and most dry eye parameters, including disease incidence, disease severity, and aqueous deficiency parameters. Also, Baldini *et al.* [11] documented no significant differences in vitamin D levels between patients with primary Sjögren's Syndrome (PSS) and controls.

## Limitations

The dry weather of Saudi Arabia might be a confounding factor in this study as it might be a causative agent of dry eye syndrome by itself. The small sample size was another limitation. Furthermore, inaccessibility of TearLab Osmometer-the gold standard test for dry eye diagnosis [19] - was the third limitation in this study because TBUT, Schirmer, and fluorescein staining alone are unsatisfactory as they correlate poorly with each other and with the cause of the disease [20].

## Conclusion

To the best of our knowledge, this study is the first one conducted in Saudi Arabia. This study did not document significant correlation between dry eye syndrome and vitamin D deficiency in Saudi patients while other studies confirmed strong association. Future studies with a larger sample size and further investigations such as TearLab Osmometer are recommended to elucidate the role of vitamin D in dry eye pathogenesis.

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