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ORIGINAL ARTICLE

Vitamin D Level with Dry Eye Syndrome in the Employees

Kadar Vitamin D dengan Sindrom Mata Kering pada Karyawan

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ABSTRACT

Background

Dry eye syndrome (DES) is the most common eye disease with a prevalence of around 5 – 50% of the worldwide population. In Indonesia alone, the prevalence of DES is around 27.5%. DES is a multifactorial disorder indicating that inflammation plays an important role in the pathophysiology of DES. The inflammation causes increased oxidative stress which can cause decreased tear production and inflammation on the ocular surface can cause an increase in excessive tear evaporation, causing instability of the tear film. Vitamin D has an anti-inflammation effect. The role of vitamin D in the eye through receptor vitamin D (VDR), which is expressed in the retinal pigment epithelium, retinal photoreceptors, ganglion cells layer, ciliary body, lens, cornea epithelium, and endothelium, as well as in aqueous humor, vitreous humor, and tears film. Vitamin D deficiency is said to have a contribution to DES. For that reason, this study aims to examine the relationship between vitamin D levels with DES.

Methods

The research design in this study was an observational analytic with a cross-sectional approach, which was followed by FK USAKTI employees in February – March 2021. Fifty-seven employees aged 25 – 60 were according to criteria and willing to take part in this study. OSDI questionnaire, Schimer's test and tear break-up time (TBUT) were used to examine DES. Examination of vitamin D by measuring 25(OH)D levels. The data were analyzed using a chi-square test with significance level $p<0.05$.

Results

The vitamin D levels examination with DES using Schimer's test was found to be unrelated ($p=0.948$), comparing vitamin D levels with the TBUT test, it was found significantly related to DES ($p=0.030$), meanwhile using the OSDI questionnaire was found to be unrelated ($p=0.285$).

Conclusions

There is a significant relationship between vitamin D levels and DES through TBUT examination.

Keywords: DES, employees, vitamin D level

ABSTRAK

Latar Belakang

Sindrom mata kering (DES) penyakit mata yang paling sering dijumpai dengan prevalensi di dunia sekitar 5 – 50%. Di Indonesia sendiri prevalensi DES sekitar 27.5%. DES disebabkan oleh banyak faktor yang menunjukkan inflamasi memegang peranan penting dalam patofisiologinya. Akibat adanya inflamasi akan menyebabkan peningkatan stress oksidatif yang dapat menyebabkan penurunan produksi air mata, dan inflamasi pada permukaan okuler dapat menyebabkan peningkatan penguapan air mata yang berlebihan sehingga menyebabkan ketidakstabilan lapisan air mata. Vitamin D mempunyai efek anti inflamasi. Peranan vitamin D pada mata melalui vitamin D reseptor (VDR) yang terekspresi pada epitel pigmen retina, fotoreseptor retina, lapisan sel ganglion, korpus siliaris, lensa, epitel dan endotel kornea, serta aquous humor, vitreous humor dan lapisan air mata. Defisiensi vitamin D dikatakan mempunyai kontribusi dalam DES, namun ada penelitian lain menyatakan tidak ada hubungan kadar vitamin D serum dengan DES. Atas dasar hal tersebut, maka tujuan penelitian ini untuk meneliti hubungan kadar vitamin D dengan DES.

Metode

Penelitian ini merupakan penelitian observasional analitik dengan design crosssectional yang diikuti oleh karyawan FK USAKTI yang dilakukan pada bulan Februari – Maret 2021. Sebanyak 57 subjek berusia 25-60 tahun sesuai kriteria dan bersedia mengikuti penelitian ini. Pemeriksaan DES dilakukan dengan kuesioner OSDI, tes Schimer dan tear break-up time (TBUT). Pemeriksaan vitamin D dengan cara mengukur kadar 25(OH)D. Analisis dengan uji chi-square dengan tingkat kemaknaan yang digunakan $p < 0.05$.

Hasil

Pada pemeriksaan kadar vitamin D dengan penderita DES dengan tes Schimer ditemukan tidak berhubungan (p=0.948), dibandingkan pemeriksaan kadar vitamin D dengan TBUT ditemukan berhubungan bermakna (p=0.030), sedangkan dengan menggunakan kuesioner OSDI ditemukan tidak berhubungan (p=0.285).

Kesimpulan

Terdapat hubungan bermakna antara kadar vitamin D dengan DES melalui pemeriksaan TBUT.

Kata Kunci: DES, karyawan, kadar vitamin D

INTRODUCTION

Dry eye syndrome (DES) is an eye disease that often occurs and impacts a person's quality of life. DES is a disease caused by many factors involving the ocular surface. This event is characterized by damage to tear film homeostasis accompanied by Ocular symptoms due to tear film instability, hyperosmolarity, damage and inflammation on the ocular surface, and neurosensory abnormalities.[1,2] This disease is most often encountered in daily practice with a prevalence of around 5–50% of the world.[1,3] In Southeast Asia, the prevalence of DES is between 20–52.4%.[4] Prevalence increases with age and women are more prevalent than men.[3,4] An epidemiological study of TFOS DEWS II states that prevalence increases between 5-30% in individuals aged over 50 years [4,5] In Indonesia, the prevalence of DES was around 27.5% in 2017.[5]

The main characteristic of DES is tear film instability, which is caused by a multifactorial chronic disease. Relevant risk factors include age, gender, race, connective tissue disorders, Sjogren's syndrome, estrogen replacement therapy, androgen hormone deficiency, medication use (antihistamines, antidepressants, anxiolytics, and isotretinoin), computer use, contact lens use, environmental conditions (pollution, low humidity, wind), while probable risk factors include diabetes, rosacea, viral infections, thyroid disease, psychiatric conditions, pterygium, low fat intake, refractive surgery, allergic conjunctivitis, inflammation, increased tear osmolarity, keratoplasty, smoking, alcohol.[3,6,7] Symptoms of DES vary from mild irritation, burning sensation, itching, red

eyes, gritty eyes (sensation like a foreign body), pain, tired eyes, and visual disturbances. Complications of DES include the risk of infection and chronic inflammation leading to perforated corneal ulcers and endophthalmitis which can result in loss of sharp vision.[3,8] In fact, several studies state that DES is a chronic inflammatory disease that shows symptoms similar to autoimmune diseases. Increased inflammatory cytokines, metalloproteinases, chemokines, and their receptors cause autoreactive T-helper cells which cause the ocular surface and lacrimal glands to become inflamed.[9] The diagnosis of DES can be made from anamnesis and several examinations such as examinations that use questionnaires including the Ocular Surface Disease Index (OSDI), Mc Monnies questionnaire, Women's Health Study Questionnaire, and Dry Eye-Related QOL score (DEQS) to assess the relevance of the occurrence of DES.[10] The OSDI questionnaire includes three domains, namely ocular symptoms, visual function, and environmental factors. The total OSDI assessment score is 0-100 with the following criteria: a score of 0-12 is said to be normal, a score of 13-22 is said to be mild, a score of 23-32 is said to be moderate, and a score of 33-100 is said to be severe. Other examinations consist of examination of the eyelid margins and meibomian glands, lissamine green staining, Matrix Metalloproteinase-9 (MMP-9) examination, Schirmer's test without prior anesthesia to assess baseline and reflection tears. This test is said to be normal if it is >15 mm if 10-15mm is said to be low normal, 6-10mm is borderline, and <6mm is said to be abnormal. However, there is another examination to describe the stability of the tear film, namely by carrying out Tear Break-up Time (TBUT) with an assessment of the normal time for dry spots to form at 15-20 seconds.[6,9,11,12] Increasingly developing technology has created a DES examination that is easier, more practical, and minimally invasive, for example, reflective meniscometry, optical coherence tomography (OCT), tear film stability analysis system (TSAS), and interferometry.[1]

Vitamin D deficiency occurs in around 1 billion of the world's population with 50% of them experiencing insufficiency.[13] It is said that the prevalence of vitamin D deficiency in South Asia is around 70% higher and varies between 6-70% in Southeast Asia.[14] The prevalence of vitamin D deficiency D in Indonesia is 63%, so even though Indonesia is a tropical country located on the equator, it does not guarantee the status of a person's vitamin D levels.[15] Humans get vitamin D3 naturally through exposure to sunlight, especially ultraviolet-B (UVB) radiation, which is a hormone precursor. Endocrine and can also be obtained from food intake.[11,15] Vitamin D plays an important role in calcium and phosphate homeostasis, especially in bone metabolism, but recently it has been said that vitamin D has anti-inflammatory effects and regulates the immune system. The effects of vitamin D in the body are through vitamin D receptors (VDR), some of which are found in the heart, vascular smooth muscle, endothelium, abdomen, brain, skin, gonads, and various cells of the immune system. VDR expression occurs in most immune cells such as T and B cells, antigen-presenting cells. Regulation of the bond between active vitamin D and VDR regulates several genes that influence the inflammatory process, immune system, cell proliferation, differentiation, and apoptosis.[11,16] The formation of vitamin D first occurs in conversion in the liver where it is formed into 25-hydroxy vitamin D (25(OH)D) which is also called calcidiol. After that, hydroxylation occurs in the kidneys to form 1,25-dihydroxy vitamin D (1,25(OH)2D) also called calcitriol. According to the Food and Nutrition Board (FNB) committee, serum 25(OH)D levels of less than 30 nmol/L are said to be deficient, while around 30–50 nmol/L are said to be insufficiency and more than 50 nmol/L are said to be normal.[17]

The causes of vitamin D deficiency are lack of exposure to sunlight (UVB) and low intake of foods or supplements containing vitamin D. Lack of outdoor activities or longer periods of working indoors, and lifestyles that avoid exposure to sunlight such as wearing heavy clothing. absorbing sunlight wearing closed clothing, and using body protection such as hats, umbrellas, and sunscreen causes less exposure to sunlight.[18,19] Vitamin D can be anti-inflammatory on the ocular surface. Previous research has stated that there is a relationship between vitamin D deficiency and chronic diseases, autoimmune diseases, malignancies, and also eye disorders.[17] Vitamin D levels are said to influence various eye pathological conditions such as myopia, age-related macular degeneration, diabetic retinopathy, and uveitis. It is even said that vitamin D deficiency contributes to DES.[9,20,21]

Over the last few decades, many studies have shown that inflammation plays an important role in the pathophysiology of DES so vitamin D deficiency will increase the incidence of dry eye syndrome.[9,20] However, research conducted in Korea stated that there was no relationship between serum vitamin D levels and DES. There are other studies stating that only people with severe vitamin D deficiency are associated with DES but this is not proven after adjusting for risk factors.[20,22,23] In this study, the subjects worked indoors so they were at greater risk of experiencing vitamin D deficiency. On this basis, the researchers intend to examine the relationship between vitamin D levels and DES in employees.

METHODS

This research is an analytical observational study with a cross-sectional design. This research looked for the relationship between vitamin D levels and DES in Faculty of Medicine Universitas Trisakti employees which was carried out in February – March 2021.

Inclusion criteria were men and women aged 25-60 years who were willing to take part in the research. Exclusion criteria are having anatomical abnormalities of the eye, using contact lenses, having a history of hypertension and DM, smoking, having a history of eye surgery, having a visual acuity of less than 6/60, having a history of long-term routine use of eye drops, having a history of malignancy, disease autoimmune (allergies), liver and kidney function disorders. The research subjects were taken using simple random sampling. The size of the research subjects was based on the infinite-finite population formula with a significance level of 95% of 1.96 and with a DES prevalence in Indonesia of 27.5%5 with a measurement accuracy of 0.05, a total of 57 research subjects were obtained. Data collection was carried out by filling out a questionnaire, where before filling in the questionnaire, the subject was explained first. The questionnaire contains information including identity (name, age, gender). The DES examination was tested using the Schirmer test, TBUT test, and OSDI questionnaire. The Schimer test is carried out using Schirmer paper with the edge of the paper folded out for a length of 5 mm. The tip of the Schirmer paper is placed in the lateral third of the lower conjunctival sac. The patient is asked to look forward and blink normally for 5 minutes and the tear-soaked strip is measured in millimeters. The results of the examination were seen from the part of the Schirmer paper that was wet with tears with a value of <10 mm, tear gland secretion was deficient. The TBUT examination assesses the breakdown of the tear film when the eye blinks. During the examination, fluorescein staining is used and the patient is asked to blink 1-2 times to even out the staining. The patient is asked not to blink, while the examiner evaluates the patient's ocular surface using a cobalt blue filter on the slit lamp. Measurements begin at the time of the last blink until fluorescein staining appears in the form of a dry spot. The normal time

for dry spots to form is 15-20 seconds. If dry spots form for ≤ 10 seconds, this could indicate a mucin deficiency in the tear film. The OSDI score is assessed with a total score of 0-100 with the following criteria: a score of 0-12 is said to be normal, and a score of >13 is a deficiency.[6,9,11] Taking 2 cc of a blood sample to check serum 25(OH)D levels using the ELISA method, it is said that if it reaches levels of 30-100 ng/ml it is sufficient/normal, whereas below this figure there is a deficiency.[17,24] The research was carried out using the chi-square test with a significance value of $p < 0.05$.

This research has been approved by the Research Ethics Commission of the Faculty of Medicine, Universitas Trisakti, Jakarta with number: 170/KER/FK/XII/2020.

RESULTS

Univariate analysis was used to determine the frequency distribution of subject characteristics in the form of gender, age, serum 25(OH)D levels, Schirmer test, TBUT, and OSDI scores.

Table 1. Data on subject characteristics (N=57)

Variable		Frequency (%)	Mean±SD
Gender			
Men	26	(41.3%)	
Women	31	(67.7%)	
Age (year)			
25 – 40	24	(42.1%)	42.0 ± 8.7
> 40	33	(57.9%)	
Serum level 25 (OH)D			
≥ 30ng/ml	11	(19.3%)	22.0 ± 11.64
< 30ng/ml	46	(80.7%)	
Schirmer test			
>10 mm	32	(56.1%)	13.13±8.91
≤10 mm	25	(43.9%)	
TBUT			
≥10 seconds	22	(38.6%)	9.08±4.56
<10 seconds	35	(61.4%)	
OSDI score			
0-12	34	(59.6%)	22±11.64
>13	23	(40.4%)	

Based on characteristic data obtained from 57 research subjects, 67.7% were dominated by women with an average age of 42.0 ± 8.7. Judging from the serum 25(OH)D levels, it was found that 80.7% had vitamin D deficiency. For the DES examination with the Schirmer test, 56.1% were normal, while for the TBUT examination, 61.4% showed disruption of the tear film and for OSDI the score was 59.6. % normal.

Table 2. Analysis of Respondent Characteristics using the Schirmer test and TBUT

	Schirmer test		p value	TBUT		p value
Variable	>10mm	≤10mm		>10 seconds	≤10 seconds	
Gender						
Men	5(19.2%)	21(80.8%)	0.174	7(26.9%)	19(73.1%)	0.860€
Women	11(35.5%)	20(64.5%)		9(29.0%)	22(71.0%)	
Age (year)						
25 – 40	18(69.2%)	8(30.8%)	0.783	10(41.7%)	14(58.3%)	0.044€
>40	12(38.7%)	19(61.3%)		12(36.4%)	21(63.6%)	
Serum level 25(OH)D						
≥30ng/ml	(27.3%)	8(72.7%)	0.948	6(54.5%)	5(45.5%)	0.030€
<30ng/ml	13(28.3%)	33(71.7%)		10(21.7%)	36(78.3%)	

€ = Chi-square test(p<0.05)

Based on Table 2 above, it can be concluded that there is no significant relationship between gender (p=0.174), age (p=0.783) vitamin D levels (p=0.948), and the Schirmer test. However, the TBUT examination showed a significant relationship with age (p=0.044) and vitamin D levels (p=0.030), whereas the relationship between gender and the TBUT examination was not found to be significant (p=0.860).

Table 3 Bivariate Analysis of Respondent Characteristics with OSDI scores

Variable	OSDI Score 0 – 12	> 13	p value€
Gender			
Men	15(57.7%)	11(42.3%)	0.783
Women	19(61.3%)	12(38.7%)	
Age (year)			
25 – 40	15(62.5%)	9(37.5%)	0.708
>40	19(57.6%)	14(42.4%)	
Serumn level 25(OH)D			
≥30ng/dl	5(45.5%)	6(54.5%)	0.285
<30ng/dl	29(63.0%)	17(37.0%)	

€ = Chi-square test (p<0.05)

Based on Table 3 above, it can be concluded that there is no significant relationship between gender (p=0.783), age (p=0.708), and vitamin D levels (p=0.285) with the OSDI questionnaire.

DISCUSSION

In this study, there was a relationship between age and TBUT examination, where 63.6% of subjects over the age of 40 years suffered from DES. DES was found to increase with increasing age.[25] The prevalence of DES increased significantly and showed a linear relationship with increasing age.[26] The prevalence of DES was said to increase by 2.0% for each decade of increasing age according to clinical diagnosis reports of dry eye and 10.5% based on the Schimer test.[4] At the age of over 40 years the main cause of DES is Meibomian Gland Dysfunction (MGD). In addition, it has been

reported that a decrease in androgens and estrogens during menopause, dyslipidemia, hypertension, and atherosclerotic disease are also associated with risk factors for DES.[4,25,27]

In this study, there were differences in the results of vitamin D deficiency with the results of the Schirmer test, TBUT, and OSDI questionnaire. In this study, vitamin D deficiency and the Schirmer test were found to be unrelated. This could be because there is no relationship with tear gland production in people with vitamin D deficiency. In the results of vitamin D deficiency and TBUT, it has been proven to have a significant relationship, this could be because vitamin D deficiency is more related to the stability of the tear film than gland production. tears. The results of this study are in accordance with research conducted in Osaka which stated that 94.6% of research subjects were diagnosed with DES by TBUT examination compared to the Schirmer test results of only 19.3%.[6] The relationship between vitamin D deficiency and the OSDI questionnaire was found to be unrelated, this could be due to the higher DES symptoms causing a higher OSDI score9, even though in this study as many as 63.0% suffered from vitamin D deficiency but still did not show any DES symptoms.

Experts agree that tear film instability is a vital mechanism causing DES which can cause symptoms and/or vision problems.[6] In DES sufferers, an increase in inflammatory cytokines, matrix metalloproteinases (MMPs), and chemokines in the tear film is found. The immune process on the ocular surface of the cornea causes the activation of protein kinase which can stimulate the transcription of nuclear factor kappa B (NF-kB), chemokines, and MMPs, which ultimately activates CD4 + T cells. T cells secrete proinflammatory factors that cause an immune response, which results in the presence of The release of T cells causes the inflammatory process to worsen and tissue damage to the cornea, conjunctiva, and lacrimal gland epithelium occurs.[20]

In addition, hyperosmolarity stress also has a direct pro-inflammatory effect on the ocular surface epithelium. This causes activation of protein kinase which stimulates the secretion of pro-inflammatory cytokines (IL-1β, TNFα, and IL-6), chemokines, MMP-3, and MMP-9, thereby causing apoptosis. The interaction of inflammatory mediators multiplies the inflammatory cascade, for example: TNFα stimulates MMP-9 and MMP-3, and MMP-9 causes damage to the corneal barrier by disrupting the corneal surface epithelium.[28]

Tears consist of water, electrolytes, mucin, proteins, and lipids. Lipids function to coat and hydrate the mucin layer. When damage to the corneal layer occurs, instability of the tear layer occurs and also causes the mucin layer in the cornea to be disrupted. As a result, the corneal surface becomes hydrophobic, thereby increasing tear evaporation and osmolarity.[20]

Conjunctival goblet cells produce mucin which stabilizes the pre-corneal tear layer. These cells also produce factors that maintain hemostasis and the immune system on the ocular surface. In DES, corneal abnormalities can occur with loss of goblet cells due to the Th1 cytokine IFN-γ which inhibits goblet cell secretion and induces cell apoptosis.[28,29]

Several studies suggest that vitamin D can be anti-inflammatory on the ocular surface of the eye. 30 The role of vitamin D in the eye is through VDR which is expressed in the retinal pigment epithelium, retinal photoreceptors, ganglion cell layer, ciliary corpus, lens, corneal epithelium, and endothelium. In addition, sources of vitamin D are also found in the aqueous humor, vitreous humor, and tear film. Recently, hydroxylation of vitamin D (CYP27B1, CYP27A1, CYP24A1) was found to occur in the corneal epithelium and endothelium, ciliary corpus epithelium, scleral fibroblasts

and the retinal pigmented epithelial cell layer, where the conversion process from 25(OH)D to active 1 occurs. ,25(OH)2D.20 Although DES is said to be caused by various factors, tear film instability, ocular surface inflammation, and hyperosmolarity play an important role.[6,20] However, several studies state that DES is also associated with single-chain polymorphisms of the VDR gene.[20]

Vitamin D acts as a paracrine or autocrine regulator through VDR. The 25(OH)D level in tears is said to be higher than in other organs. The role of vitamin D inhibits corneal inflammation by inhibiting the migration of Langerhans cells to the cornea, limiting excessive production of proinflammatory mediators such as interleukin, TNFα.[20]

Several studies do state that vitamin D can be anti-inflammatory on the ocular surface, but research conducted by Jee et.al., states that the effect of serum vitamin D on the cornea can be limited due to the blood supply to the cornea. The retina and macula receive more blood supply than the lens and cornea, whereas is known the effect of vitamin D reaches the eye through the bloodstream. [30] In addition, the explanation by Waterhouse et.al., states that DES may be related to VDR dysfunction and not just with 25(OH)D levels. Measuring only 25(OH)D cannot fully describe the relationship between vitamin D and various diseases, so it may be considered to measure the results of vitamin D metabolites. 30,31 In addition, ocular vitamin D levels were not examined in this study so serum vitamin D levels cannot be measured. can describe overall ocular vitamin D levels. This was also found in research conducted by Jee et.al.[31,33]

Providing systemic oral vitamin D supplementation can help some DES sufferers, especially those who are unresponsive to conventional treatment and those with vitamin D deficiency. [20,34,35] However, the effect of oral vitamin D supplementation to prevent or improve the signs and symptoms of DES still needs to be proven again. It is also necessary to pay attention to the administration of topical vitamin D. Topical administration of vitamin D was found to be associated with an antibacterial response on the ocular surface.[35] In animal studies using mice, it was stated that topical administration of vitamin D preparations was found to be able to inhibit Langerhans cell migration and inhibit pro-inflammatories such as the cytokinin IL-1α and tumor necrosis factor-α (TNFα).[36] However, until now there has been no research on the effects of topical vitamin D alone.[35] The limitation of this research is that the researchers did not ask about the length of time the research subjects worked in air-conditioned rooms, the use of laptops, gadgets and length of exposure to sunlight, use of sunblock in their daily lives.

CONCLUSION

There is a significant relationship between vitamin D levels and DES with TBUT examination. However, giving oral vitamin D supplementation to improve DES still needs further research, even though vitamin D has been proven to be anti-inflammatory.

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AUTHORS CONTRIBUTION

EM was involved in preparing the concept and research design, manuscript preparation, data collection, manuscript preparation, and corresponding author. M was involved in data collection,

analysis, and interpretation of results. EK and NP were involved in data collection, preparation, and manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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