

# Dry Eye and its Relationship with Status of Serum Calcium in the Body at a Tertiary Care Institute: A Case Control Study

Mrunal Patil<sup>1</sup>, Dhiraj Balwir<sup>2\*</sup>, Ajit Khune<sup>3</sup>, Saurabh Dhewale<sup>4</sup>

<sup>1</sup>Dean and Professor, Department of Ophthalmology, Dr. Vasant Rao Pawar Medical College Hospital & RC, Nashik - 422003, India; drmrunal\_patil@yahoo.com

<sup>2</sup>Professor and Head, Department of Ophthalmology, Dr. Vasant Rao Pawar Medical College Hospital & RC, Nashik - 422003, India

<sup>3</sup>Associate Professor, Department of Ophthalmology, Dr. Vasant Rao Pawar Medical College Hospital & RC, Nashik - 422003, India

<sup>4</sup>PG Resident, Department of Ophthalmology, Dr. Vasant Rao Pawar Medical College Hospital & RC, Nashik - 422003, India; dsaurabh89@gmail.com

## Abstract

**Background:** Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of dryness, grittiness, redness, burning sensation or any discomfort, visual disturbance and tear film instability leading to potential damage to ocular surface. The tear film consists of three layers starting from within outwards mucus, the aqueous layer and the lipid layer. The tear film and ocular surface form a complex and stable system that can lose its equilibrium through numerous disturbing factors. Studies which also involve tests of tear functions including Schirmer's test, Tear break-up time, Fluorescein staining for determination of dry eye have found generally low prevalence rates. Hence the physiology of tear film and its binding with the eye shows that there is some involvement of serum calcium level with dry eye. The present study encourages us to assess the role of serum calcium level with patients of dry eye. **Aims and Objective:** To assess the role of calcium with dry eye. **Material and Methods:** Total 90 subjects (30 cases and 60 controls) who met the selection criteria were included in the study. Serum analysis has been done for calcium level in the body in the patients of dry eye. The study was conducted between August 2014 to November 2016. **Results:** The lower serum level of calcium was significantly associated with dry eyes in the study. **Conclusion:** Calcium plays an important role in the causative mechanism of dry eye in the patients of dry eye disease.

**Keywords:** Calcium, Dry Eye, Serum Level, Tear Film

## 1. Introduction

Dry eye is one of the most prevalent ocular surface disease in the world occurring from 4.4% to as high as 50% of middle aged and older people<sup>1,2</sup>. The tear film consists of three layers starting from within outwards mucus, the aqueous layer and the lipid layer. The tear film and ocular surface form a complex and stable system that can lose its equilibrium through numerous disturbing factors<sup>3</sup>. The earliest corneal manifestation of xerophthalmia is instability of the precorneal tear film which can lead to a dull and lustreless corneal appearance<sup>4</sup>. There are studies demonstrating that corneal epithelial cells contain VDR and 1 alpha hydroxylase mRNA and that there are

significant Vitamin D metabolite concentrations in both the aqueous and vitreous humour. In addition, both 25(OH)D<sub>3</sub> and 1,25(OH)D<sub>3</sub> can enhance corneal epithelial barrier function and Vitamin D supplements enhance corneal occluding expression<sup>5</sup>. The role of vitamin D and calcium go hand in hand. Vitamin D is responsible for the calcium and phosphorus levels in the body.

Serum calcium status in the serum is suitable for studying its association with systemic conditions. However, it would be beneficial to obtain tissue specific vitamin D status for localized conditions such as ocular surface disease. There is increasing evidence regarding extra-renal synthesis and tissue specific effects of vitamin D<sub>3</sub> in other tissues<sup>6</sup>, including the eye<sup>7-10</sup>. The cells and

tissues in the eye are responsive to 1,25-dihydroxyvitamin D since VDR is present in the epithelium of the cornea, lens and ciliary body, corneal endothelium, retinal pigment epithelium, ganglion cell layer and photoreceptors of the human eye<sup>7-11</sup>.

The present study "Dry Eye and its Relationship with Status of Vitamins in the Body at a Tertiary Care Institute: A Case Control Study" was conducted to assess the role of serum level of calcium associated with dry eyes.

## 2. Aims and Objective

To assess the role of calcium with dry eye.

## 3. Material and Methods

Study was conducted in Department of Ophthalmology, Dr Vasantrao Pawar Medical College, and Nasik after Institutional review board approval. Total of 90 patients (30 cases and 60 controls) were taken in the study and their serum calcium level were measured.

### Study Design and Study Population

- Study design: A case control study.
- Study settings: Department of Ophthalmology, Medical College and Hospital, Tertiary care centre.
- Duration of the study: Period of Two years from August 2014 to November 2016.
- Sample size: 90 (30 cases and 60 controls).
- Study Participants.

## 4. Eligibility Criteria

### 4.1 Inclusion Criteria

#### 4.1.1 Inclusion Criteria for Cases

- Diagnosis of Dry Eye Disease based on following criteria:
  - Presence of dry eye symptoms.
  - Presence of qualitative and quantitative disturbance of the tear film in one or both eyes (Schirmer's test results <5mm or tear film break-up time <5 seconds).
  - Presence of conjunctival and corneal epithelial damage (total staining score, >3 points) in one or both eyes.
  - Adult Patients (>18 years of age) irrespective of gender satisfying the above criteria of dry eye disease.
  - Patient willing to take part in the study.

### 4.2.2 Inclusion Criteria for Controls

- Patients not diagnosed as Dry eye disease based on the above mentioned criteria.
- Adult Patients (>18 years of age) with group matching done for age and gender.
- Patient willing to take part in the study.

### 4.2 Exclusion Criteria for Both Cases and Controls

- Contact lens wearers- within 12 hours of any study visit.
- Patient who underwent LASIK surgery/cataract surgery.
- Patients diagnosed with Sjogren's syndrome, Rheumatoid arthritis and Parkinson's disease.
- Clinically significant eyelid deformity or eyelid movement disorder caused by conditions such as notch deformity, incomplete lid closure, entropion, ectropion, hordeola, or chalazion.
- Patients taking medications such as anti-histaminics, TCAs, OC pills, anti-hypertensives, diuretics or tetracyclines - within 3 weeks of any study visit.
- Punctal cauterization or punctal plug placement within 60 days of screening.
- Abnormal nasolacrimal drainage.
- Any infective ocular diseases.
- Any allergies.
- Pregnancy.

## 5. Methodology

After satisfying inclusion and exclusion criteria, 30 cases of dry eye with age and gender matched 60 controls were enrolled in the study.

Basic information was taken from all study participants as per proforma. All participants underwent clinical as well as ophthalmic examination as follows

- History.
- Visual Acuity (with Log MAR chart).
- Anterior Segment Examination.
- Schirmer's Test.
- TFBUT (Tear Film Break Up Time).
- Ocular Surface Staining.
- Tonometry.
- Fundus Examination.

After examination, patients' serum level of calcium have been measured.

### 5.1 History

A thorough and detailed history of all selected patients was taken as per proforma of the study. Patient’s age, sex and associated ocular complaint was noted.

### 5.2 Ocular Examination

- A one time examination of the cases and controls was done and no follow-ups were included in the study.
- Best corrected visual acuity (BCVA) was recorded in both the eyes with the use of LogMAR chart in the OPD.
- Intraocular Pressure was measured using Goldmann Applanation tonometer.
- A thorough and detailed examination of the anterior segment was performed on the slit lamp.
- Both direct and consensual papillary reactions were checked.
- Following which pupils were dilated using 0.8% w/v tropicamide with 5.0% w/v phenylephrine drops 2 to 3 times for 20 to 30 mins.
- (Phenylephrine was avoided in hypertensive patients).
- A detailed fundus examination was done by direct ophthalmoscope, indirect ophthalmoscope 20D lens and Slit-lamp biomicroscopy with +90D lens (conventional ophthalmoscopy) in fully dilated pupil.
- Schirmer’s test has been done in both eyes using 41 no. Whattmann filter paper and readings has to be taken after 5mins.
- After fluoresceinstaining, Tear Film Break Up Time (TF-BUT) and Ocular surface Staining score was measured with the help of cobalt blue filter of slit lamp.

### 5.3 Serum Analysis

Blood samples were collected for serum level of calcium and role of calcium will be compared among cases and controls.

Serum calcium level is analysed with the help of chemi and bioluminescence principle and with the use of instrument LUMAX MODEL 4101 CLIA strip reader.

### 5.4 Statistical Analysis

Appropriate statistical analysis will be done for

interpretation of given objectives. Independent t test was applied to mean serum level of calcium in cases and controls. A probability value (p value) ≤ 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 17.

## 6. Results

In the present study, there were 30 cases and 60 controls. The case to control ratio was 1:2. Out of 90 patients, 33.33% i.e., 30 patients were cases and 66.67% i.e., 60 patients were controls which were enrolled in the study (Table 1).

**Table 1.** Distribution of cases and controls

Group	No. of Patient	Percentage
Case	30	33.33%
Control	60	66.67%
<b>Total</b>	<b>90</b>	<b>100.00%</b>

In the present study, out of 30 cases of dryness 11 (36.67%) were males and 19 (63.33%) were females. The male to female ratio (0.58:1) showing significant female preponderance in cases of dry eye. Out of 60 controls in the study, 31 (51.67%) were males and 29 (48.33%) were females showing nearly equal distribution amongst them (Table 2).

**Table 2.** Gender wise distribution of cases and controls

Gender	Case ( Dryness )		Control ( No Dryness )	
	No	%	No	%
Male	11	36.67%	31	51.67%
Female	19	63.33%	29	48.33%
<b>Total</b>	<b>30</b>	<b>100.00%</b>	<b>60</b>	<b>100.00%</b>

In the present study, out of 30 cases of dryness, 17 (56.67%) were vegetarian and 13 (43.33%) were taking mixed diet. Out of 60 controls, 28 (46.67%) were vegetarian and 32 (53.33%) were taking mixed diet. Among 30 cases, those taking vegetarian diet were more prone to dryness rather than those taking mixed diet. It is observed in the present study that those taking vegetarian diet were 1.30 times more prone to dryness than those taking mixed diet (Table 3).

**Table 4.** Mean difference of serum calcium levels in cases and controls

Parameter	Group	N	Mean	Std. Deviation	t	df	p-value	Significance
Sr. Calcium	Case	30	8.52	0.67	-4.509	88	<0.0001	Highly Significant
	Control	60	9.01	0.36				

**Table 3.** Diet wise distribution of cases and controls

Diet	Case ( Dryness )		Control ( No Dryness )	
	No	%	No	%
Veg	17	56.67%	28	46.67%
Mixed	13	43.33%	32	53.33%
<b>Total</b>	<b>30</b>	<b>100.00%</b>	<b>60</b>	<b>100.00%</b>

After applying 'Independent t test' for difference between means of Cases and Controls we got significant p- value < 0.0001 which is Highly Significant (Table 4).

## 7. Discussion

In the present study, there were 30 cases and 60 controls. The case to control ratio was 1:2. Out of 90 patients, 33.33% i.e., 30 patients were cases and 66.67% i.e., 60 patients were controls which were enrolled in the study. In our study all patients including cases and controls were in the age group of 18 to 58 years. In the present study, out of 30 cases of dryness 11 (36.67%) were males and 19 (63.33%) were females. The male to female ratio (0.58:1) showing significant female preponderance in cases of dry eye. Out of 60 controls in the study, 31 (51.67%) were males and 29 (48.33%) were females showing nearly equal distribution amongst them.

Similar findings were obtained in the studies done by Schaumberg DA, et al<sup>12,13</sup> and Yazdani C, et al<sup>14</sup>. The weight of the evidence from large epidemiological studies done by Schein OD<sup>15</sup> and Munoz B<sup>16</sup> indicates that female sex and older age increase the risk for dry eye. In the present study, out of 30 cases of dryness, 17(56.67%) were vegetarian and 13(43.33%) were taking mixed diet. Out of 60 controls, 28(46.67%) were vegetarian and 32(53.33%) were taking mixed diet. Among 30 cases, those taking vegetarian diet were more prone to dryness rather than those taking mixed diet. It is observed in the present study that those taking vegetarian diet were 1.30 times more prone to dryness than those taking mixed diet. Dadaci Z, Yildirim P, Yoon SY found that Serum Calcium levels were also reported to be associated with some ocular surface conditions such as dry eye and allergic conjunctivitis<sup>17-19</sup>. Suzuki T, Dang ST states that in vivo reports provide evidence concerning the anti-inflammatory and immunomodulatory roles of serum calcium in the corneal region<sup>20,21</sup>. Rohit Shetty found correlation between serum vitamin D and ultimately with serum calcium in evaporative dry eye disease<sup>22</sup>. Shetty R, Deshpande K, Deshmukh R, Jayadev C, Shroff R found that Inflammation aggravated by vitamin D deficiency and serum calcium deficiency results in an altered

epithelial profile, Bowman layer damage, recruitment of dendritic cells, and altered sub-basal nerve plexus features in patients with chronic dry eye disease<sup>23</sup>.

## 8. Conclusion

- Serum calcium is mainly seen affected by significantly decreased levels and having role in the association of dry eye.
- Hence the patients with dry eyes should be approached with a holistic view of assessing the serum calcium levels and managing them with holistic approach.

## 9. References

1. McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology*. 1998; 105:1114-9. <https://doi.org/10.1016/S0161-6420%2898%2996016-X>
2. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol*. 2000; 118:1264-8. <https://doi.org/10.1001/archophth.118.9.1264> PMID:10980773
3. Brewitt H, Sistani F. Dry eye disease: The scale of the problem. *Surv Ophthalmol*. 2001; 45(Suppl 2):S199-202. <https://doi.org/10.1016/S0039-6257%2800%2900202-2>
4. Lapalus P, Fredj-Reygrobellet D, Delayre T. Effect of vitamin B12 on the healing of corneal wounds in the rabbit. *Contactologia*. 1988; 10:73-5.
5. Wolff E. Mucocutaneous junction of lid margin and the distribution of the tear fluid. *Trans Ophthalm Soc*. 1946; 66:291-308.
6. Plum LA, DeLuca HF. Vitamin D, disease and therapeutic opportunities. *Nat Rev Drug Discov*. 2010; 9:941-55. <https://doi.org/10.1038/nrd3318> PMID:21119732
7. Adams JS, Hewison M. Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. *Arch Biochem Biophys*. 2012; 523:95-102. <https://doi.org/10.1016/j.abb.2012.02.016> PMID:22446158 PMCid:PMC3361592
8. Alsalem JA, Patel D, Susarla R, Coca-Prados M, Bland R, Walker EA, et al. Characterization of vitamin D production by human ocular barrier cells. *Invest Ophthalmol Vis Sci*. 2014; 55:2140-7. <https://doi.org/10.1167/iovs.13-13019> PMID:24576880
9. Lin Y, Ubels JL, Schotanus MP, Yin Z, Pintea V, Hammock BD, et al. Enhancement of vitamin D metabolites in the eye following vitamin D3 supplementation and UV-B irradiation. *Curr Eye Res*. 2012; 37:871-8. <https://doi.org/10.3109/02713683.2012.688235> PMID:22632164 PMCid:PMC3572765
10. Reins RY, McDermott AM. Vitamin D: Implications for ocular disease and therapeutic potential. *Exp Eye Res*. 2015; 134:101-10. <https://doi.org/10.1016/j.exer.2015.02.019> PMID:25724179 PMCid:PMC4426046
11. Yin Z, Pintea V, Lin Y, Hammock BD, Watsky MA. Vitamin

- D enhances corneal epithelial barrier function. *Invest Ophthalmol Vis Sci.* 2011; 52:7359–64. <https://doi.org/10.1167/iovs.11-7605> PMID:21715350 PMCID:PMC3183972
12. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol.* 2003; 136:318–26. [https://doi.org/10.1016/S0002-9394\(03\)2803-6](https://doi.org/10.1016/S0002-9394(03)2803-6)
  13. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: Estimates from the Physicians' Health Studies. *Arch Ophthalmol.* 2009; 127:763–68. <https://doi.org/10.1001/archophthol.2009.103> PMID:19506195 PMCID:PMC2836718
  14. Yazdani C, McLaughlin T, Smeeding JE, Walt J. Prevalence of treated dry eye disease in a managed care population. *Clin Ther.* 2001; 23:1672–82. [https://doi.org/10.1016/S0149-2918\(01\)29801-3](https://doi.org/10.1016/S0149-2918(01)29801-3)
  15. Schein OD, Hochberg MC, Munoz B, et al. Dry eye and dry mouth in the elderly: A population-based assessment. *Arch Intern Med.* 1999; 159:1359–63. <https://doi.org/10.1001/archinte.159.12.1359> PMID:10386512
  16. Munoz B, West SK, Rubin GS, et al. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. *Arch Ophthalmol* 2000; 118:819–25. <https://doi.org/10.1001/archophth.118.6.819> PMID:10865321
  17. Dadaci Z, Borazan M, Kiyici A, OncelAcir N. Plasma vitamin D and serumtotal immunoglobulin E levels in patients with seasonal allergicconjunctivitis. *Acta Ophthalmol.* 2014; 92:443–6. <https://doi.org/10.1111/aos.12398> PMID:24667068
  18. Yildirim P, Garip Y, Karci AA, Guler T. Dry eye in vitamin D deficiency: More than an incidental association. *Int J Rheum Dis.* 2016; 19:49–54. <https://doi.org/10.1111/1756-185X.12727> PMID:26269110
  19. Yoon SY, Bae SH, Shin YJ, Park SG, Hwang SH, Hyon JY, et al. Low serum 25-hydroxyvitamin d levels are associated with dry eye syndrome. *PLoS One.* 2016; 11:e0147847. <https://doi.org/10.1371/journal.pone.0147847> PMID:26807908 PMCID:PMC4726745
  20. Suzuki T, Sano Y, Kinoshita S. Effects of 1-alpha,25-dihydroxyvitamin D3 on Langerhans cell migration and corneal neovascularization in mice. *Invest Ophthalmol Vis Sci.* 2000; 41:154–8. PMID:10634615
  21. Dang ST, Lu XH, Zhou J, Bai L. Effects of 1alpha, 25-dihydroxyvitamin D3 on the acute immune rejection and corneal neovascularization in high-risk penetrating keratoplasty in rats. *Di Yi Jun Yi Da Xue Xue Bao.* 2004; 24:892–6, 903.
  22. Shetty R, Sethu S, Deshmukh R, Deshpande K, Ghosh A, Agrawal A, Shroff R. Corneal dendritic cell density is associated with subbasal nerve plexus features, ocular surface disease index, and serum vitamin D in evaporative dry eye disease. *Biomed Res Int.* 2016; 4369750. <https://doi.org/10.1155/2016/4369750>
  23. Shetty R, Deshpande K, Deshmukh R, Jayadev C, Shroff R. Bowman break and subbasal nerve plexus changes in a patient with dry eye presenting with chronic ocular pain and vitamin D deficiency. *Cornea.* 2016 May; 35(5):688–91. <https://doi.org/10.1097/ICO.0000000000000785> PMID:26890669

**Cite this article as:** Patil M, Balwir D, Khune A, Dhewale S. Dry Eye and its Relationship with Status of Serum Calcium in the Body at a Tertiary Care Institute: A Case Control Study. *MVP Journal of Medical Sciences* 2018; 5(1):82-86.