

# The Relationship Between Dry Eye in Adults with Indications for Kidney Transplantation and Influence Factors

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**Purpose:** Patients with end-stage renal failure are susceptible to dry eye disease. This study explores the relationship between dry eye disease and influence factors.

**Patients and Methods:** The control group consisted of 57 healthy subjects who were kidney donors. They were of the same age and sex as the kidney transplant recipients. The outcome variable was the dry eye condition of the participants. The Schirmer test confirmed dry eye disease, TBUT (breakup time test), and the Eye Surface Disease Index (OSDI) questionnaire, using linear regression to evaluate the association.

**Results:** The total number of subjects was 146 (89 kidney recipients and 57 kidney donors). When univariate analysis found the level of visual acuity, the age group involved was statistically significant, while the other factors were not statistically significant. In multi-variable logistic regression analysis, age (odds ratio: 2.8,  $p < 0.05$ ), smoking history (odds ratio: 0.1,  $p < 0.05$ ), corneal conjunctival calcification (odds ratio: 0.2,  $p < 0.05$ ); central corneal thickness (odds ratio: 1.02,  $p < 0.05$ ) is considered to be an influence factor for disease progression.

**Conclusion:** Age group, smoking history, corneal central thickness, and conjunctival calcification are factors for dry eye disease in patients preparing to receive a kidney. These results reinforce the evidence for multifactorial dry eye disease in patients with renal impairment.

**Keywords:** dry eye, renal failure, renal transplant, Hanoi Vietnam

## Introduction

Dry eye is a common disorder characterized by ocular surface disease. They are characterized by tear film instability and associated ocular symptoms, including tear film instability and the tear film's increased osmolarity. Neurosensory abnormalities play a role in tears, inflammation, and damage to the ocular surface.<sup>1</sup> Dry eyes are familiar in all ages and social backgrounds, but those at high risk are the elderly, postmenopausal women, or people with autoimmune and chronic diseases.<sup>2,3</sup> Classification of dry eyes includes three causes: dehydration, increased evaporation, combined dehydration, and increased evaporation. The classification tables have been shown that the cause of increased evaporation accounts for a more significant proportion than the lack of water, accounting for about 70%.<sup>3-5</sup>

Dry eye is one of the most frequently stated problems with the patient who often has end-stage chronic renal failure.<sup>6-8</sup> Dry eye has existed as a health problem for many years. Therefore, dry eye disease is one of the reasons why patients with end-

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stage renal failure have to visit regular eye exams, causing considerable costs in terms of treatment costs and reducing the quality of life.

Although some research has been carried out in Vietnam on dry eye, no studies have found which dry eye in renal failure patients with indications for kidney transplantation and the correlated factors. This paper aims to explore “The relationship between dry eye in adults with indications for kidney transplantation and influence factors”.

## Patients and Methods

Ethical approval was obtained according to Decision No. 467/GCN-HDDDNCSYHN-ĐHYHN dated 04/05/2021, Hanoi Medical University, Vietnam. All patients provided written informed consent, and that this study was conducted following the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The formula for calculating sample size uses the formula for determining the sample size of a proportion of the World Health Organization.<sup>9</sup>

The participants were divided into two groups based on the study group included 89 patients with end-stage renal failure with an indication for kidney transplantation; the control group consisted of 57 kidney donors who had undergone health screening and were eligible for surgery, they are the same age and sex as the recipients. We chose to analyze the results in the left eye.

## Inclusion Criteria

Patients diagnosed with renal failure grade 3 to 4 indicated for kidney transplantation with glomerular filtration rate < 60 mL/min/1.73m<sup>2</sup> according to the formula of KDIGO (Kidney Disease Improving Global Outcomes 2012).<sup>10</sup> Chronic kidney disease includes chronic glomerulonephritis and other reasons such as hypertension, polycystic kidney, chronic pyelonephritis, lupus, gout, diabetes. Sex, the age at the time of the study was over 18, and the time of disease detection was different were studied.

## Exclusion Criteria

Acute systemic comorbidities such as sepsis, respiratory failure, pneumonia, stroke. In the eyes, there are inflammatory diseases of the ocular surface, acute and chronic glaucoma, chronic uveitis, degenerative eye disease, keratoconjunctivitis, history of surgical eye, contact lens wear, diagnosis, and previous treatment.

## Variables

The main study variable was dry eye disease in all subjects. The diagnostic criteria for dry eye are based on three methods, including the Schirmer test, TBUT (time break-up test), and OSDI (Ocular surface disease index) questionnaire.<sup>11</sup> Systemic factors include age (years), sex (male or female), body nutritional status as calculated by BMI = weight / (height / 100)<sup>2</sup> in three levels of ≤ 18.5, 18.5–25, and ≥ 25.<sup>12</sup> Age groups were divided into three age groups: ≤ 30 years old, 31–40 years old, and ≥ 41 years old. Previous smoking habits were noted as a predisposing factor. Blood samples were collected to determine serum calcium as measured by the enzymatic method on an Olympus AU 680 (Tokyo, Japan). Serum calcium as measured by the enzymatic method on an Olympus AU 680 (Tokyo, Japan).

## Protocol

All participants responded to an OSDI (Ocular Surface Disease Index) questionnaire to assess dry eye disease functional symptoms. This questionnaire is reliable for assessing dry eye symptoms.<sup>11</sup> Perform the Schirmer I test (without anesthetic) to quantify tear secretion with a 35 x 5mm filter paper strip, which is used to measure the number of tears produced over 5 minutes. After five minutes of the Schirmer I test, we conducted a test to measure the break-up time of the tear film TBUT (test break-up time). We use the sterile fluorescent dye Fluorescein. The participants look upward, and the fluorescein paper was gently touched to the lower eyelid conjunctiva and then removed. Participants blinked three times and then looked straight ahead without blinking. The tear film was observed under the cobalt blue filter light of a slit lamp biological microscope, and the time interval between the last blink and the appearance of the first dry spot in seconds was accepted as TBUT. The eye is diagnosed as dry when the Schirmer value is less than 10 mm, the TBUT is less than 10 seconds, or the total OSDI score is > 35 points.<sup>12</sup>

Best-corrected visual acuity using the Snellen electronic table at a distance of 5m, in logMAR units, divided into three levels: group reaching maximum visual acuity 0.0, group achieving visual acuity 0.1, and group 3 remaining visible acuity levels. Apply one drop of Alkain 0.1% (Alcon) to each eye, Goldmann tonometer Fluorescein stain, model BQ-900 (Haag-Streit; Haag Streit, Bern Switzerland) to obtain IOP readings from each eye. Evaluation of the anterior segment, including cornea, anterior chamber, iris, pupil, and vitreous by CSO microscope

(Italy). Mydrin-P pupil dilation evaluates the posterior segment, including vitreous, optic disc, central retina.

## Data Processing

Data entry was completed using EpiData software 3.1 (EpiData, Odense, Denmark). Statistical analysis and data cleaning with STATA 16.0 (Stata Corp, College Station, TX, USA). Quantitative data are presented as mean and standard deviation, and qualitative data are presented as absolute values and percentages. Test of normal distribution, compare the mean of two groups by t-student test, of many groups by ANOVA test. For non-normal distribution, test the mean of two independent groups using the Wilcoxon-Mann-Whitney test and the mean of more than two separate groups using the Kruskal-Wallis test. Compare two proportions of one group by Chi-square test, two independent groups by Fisher test with qualitative variables. Using logistic regression equation to evaluate the relationship between dry eye disease with several independent variables in the system and eyes.

## Results

We compared the sign of dry eye status and factors that may affect the dry eye in patients with renal failure and healthy participants. The differences between the transplant group and donor group are highlighted in Table 1.

We used the SchirmerI test, TBUT tear film break time, and OSDI scores to assess the degree of dry eye in the kidney transplant group (Figure 1).

As Figure 1 shows, there is a significant difference between the dry and non-dry groups ( $p < 0.05$ , Wilcoxon signed-rank test) (Table 2).

**Table 1** Some Characteristics of the Disease Group and the Control Group

Variables	Transplant Group		Donor Group		P
	N	Mean (SD)	N	Mean (SD)	
SchirmerI (mm)	89	14.3(7.2)	57	19.4(7.9)	<0.001**
TBUT (seconds)	89	8.1(4.9)	57	18.3(6.2)	<0.001**
OSDI score	89	14.4(7.8)	57	12.6(9.3)	<0.001**
Age (year)	89	37.6(11.3)	57	32.3(7.8)	<0.05**
BMI score	89	21.2(2.6)	57	22.2(1.4)	<0.05*
BCVA (logMAR)	89	0.2(0.2)	57	0.1(0.1)	<0.05**
IOP (mmHg)	89	14.7(2.1)	57	15.3(1.3)	<0.05*
CCT ( $\mu\text{m}$ )	89	531.5(31.3)	57	548.2(27)	<0.05*

**Notes:** \*t-test, \*\*Wilcoxon signed-rank test.

**Abbreviations:** TBUT, test break-up time; OSDI, ocular surface disease index; BMI, body mass index; BCVA, best-corrected vision acuity; IOP, intraocular pressure; CCT, central corneal thickness.

The correlational analysis results show a negative correlation between the Schirmer test and visual acuity grade, TBUT test with age group, and visual acuity group in Table 2. There was a positive correlation between OSDI score and age group and visual acuity group ( $p < 0.05$ ) (Table 3).

The data featured in this table is the regression coefficient between the incidence of dry eye disease with age group, previous smoking habits, conjunctival calcification, and corneal central thickness in patients with end-stage renal failure were statistically significant ( $p < 0.05$ ).

## Discussion

It is the first study conducted on renal failure patients with indications for kidney transplantation in Vietnam. The study results showed that the incidence of dry eye disease was significant with age, smoking history, and central corneal thickness. This study provides evidence on the prevalence of dry eye disease and, at the same time, indicates some related factors, thereby providing guidelines for the treatment of dry eye disease in these patients.

Prior studies have noted the importance of the relationship between dry eye disease and age.<sup>13–15</sup> This phenomenon is due to the decline in the endocrine, leading to disorders of the accessory tear glands. In patients with end-stage renal failure, in addition to age, renal failure also increases the degree of damage to the tear glands.<sup>6</sup> Urea concentration increases in tears, decreased tear secretion after dialysis causes an increase in tear osmolarity. This phenomenon stimulates epithelial cell inflammation, inflammatory cytokines, and background metalloproteinases (MMPs) cause damage to the ocular surface, loss of goblet cells, and loss of mucin cells, resulting in lacrimal instability.<sup>16</sup> Prolonged kidney failure, along with aging, makes dry eyes worse.

A strong relationship between dry eye and secondhand smoke has been reported in the literature.<sup>17</sup> Secondhand smoke irritates the surface of the ocular, which, when prolonged, continuously activates T cells. This process, in turn, triggers the call of other T cells, causing local inflammation. Cytokines are released in tears as subsequent inflammation irritates the ocular surface and blocks sensory signals from the ocular surface to the lacrimal gland, resulting in decreased tear secretion and the development of dry eye syndrome.<sup>18</sup> Our study found that smoking habits, although at the time of examination, patients with renal failure were no longer using them, were still a risk factor for dry eye disease. This information is recommended for patients with renal failure of all stages.

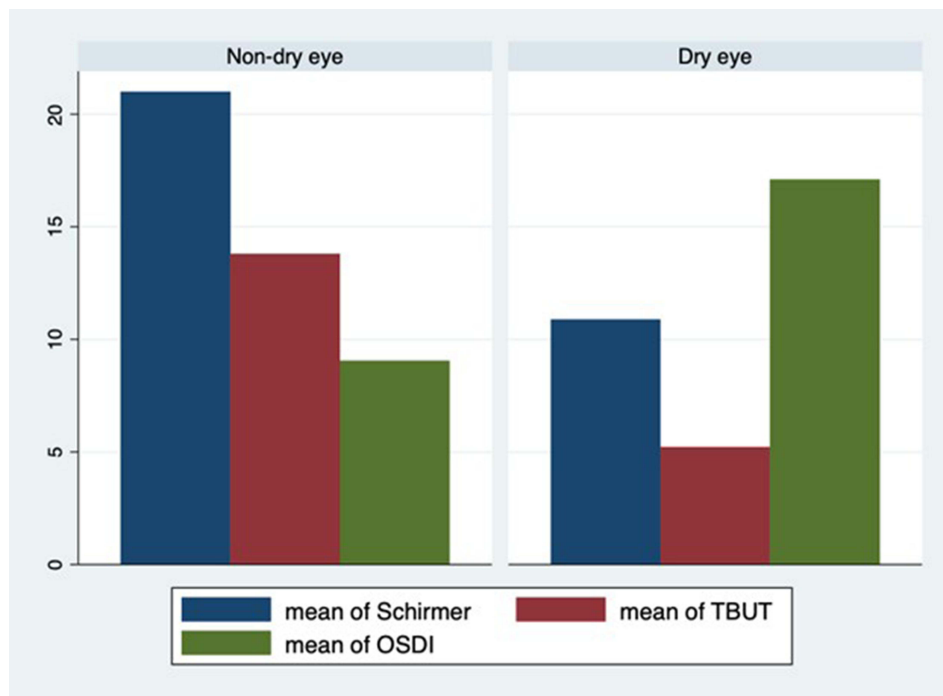


Figure 1 Distribution of mean values of dry eye tests in the kidney transplant group.

The current study found that dry eyes can cause calcium deposition in the conjunctiva.<sup>16</sup> In contrast, calcified deposit on the conjunctiva in patients with renal failure on dialysis results from the accumulation of toxic materials in the systemic and metabolic changes that disrupt the stability of tear film, disrupting the regular distribution of tears across the cornea. Calcium deposition induces inflammatory responses and increases tear permeability. In our study, the correlation between dry eye and corneal calcification was significant. This finding was also reported by Aktas’s study.<sup>12</sup> This outcome was contrary to Ozdemir et al, who found no relationship between conjunctival calcification and dry eye.<sup>19</sup> This difference is probably due to different criteria for evaluating dry eyes. The author used additional measures of Rose-Bengal staining to assess the degree of dry eyes and two standards, Schirmer and TBUT.

Szczotka-Flynn et al showed that vision loss is more pronounced in patients with dry eyes than decreased contrast sensitivity.<sup>20</sup> This differs from the findings presented here in our study; the visual acuity level of patients with renal failure was not affected by dry eye. A possible explanation for this might be that the dry eye condition in our study group is still not enough to affect the visual acuity and the vision loss is due to other damage factors in the eye.

The results of Liu’s study showed a thinning of the cornea with dry eye.<sup>21</sup> This sign occurs because chronic inflammation activates the immune system to damage corneal endothelial cells, especially in patients with renal failure on dialysis. This study confirms that dry eye is associated with central corneal thickness.

Our finding contradicts previous studies, which have suggested that serum calcium levels are significant in dry

Table 2 Single-Variable Correlation Between Dry Eye Tests with Some Factors in the Kidney Transplant Group

Dry Eye Tests	Schirmer I		TBUT		OSDI Score	
	Coefficient	p	Coefficient	p	Coefficient	p
History of smoking	0.2	>0.05	0.2	>0.05	-0.1	>0.05
Age group	-0.1	>0.05	-0.3	<0.05	0.2	<0.05
VA grade	-0.3	<0.05	-0.2	<0.05	0.3	<0.001
Calcification	0.03	>0.05	0.2	>0.05	-0.2	>0.05
CCT	-0.2	>0.05	-0.1	>0.05	-0.02	>0.05

Abbreviations: VA groups, visual acuity grade; CCT, central corneal thickness; TBUT, test break-up time; OSDI, ocular surface disease index.

**Table 3** Prevalence of Dry Eye with Some Factors in Renal Failure Group: Logistic Regression

Dry Eye	OR	95%-CI	P
Sex	1.5	[0.4, 5.3]	>0.05
Age groups	2.8	[1.2, 6.5]	<0.05
Smoking history (yes/no)	0.1	[0.02, 0.5]	<0.05
Calcification (yes/no)	0.2	[0.05, 0.9]	<0.05
Visual acuity grade (logmar)	1.6	[0.9, 3.3]	>0.05
Corneal center thickness	1.02	[1.0, 1.04]	<0.05
Serum calcium test	1.2	[0.3, 5.9]	>0.05

eye disease. When serum calcium levels decrease, dry eye disease worsens.<sup>22</sup> In our study, calcium concentration did not correlate with the degree of the patient's dry eye. The constant serum calcium levels could explain this in patients with renal failure undergoing hemodialysis, so serum calcium levels are unstable.

Our study's limitation is that the case-control study's design requires a review of several factors in the past, leading to repeat errors and some retroactive elements that cannot be performed in the control group. In addition, in our research, the Rose-Bengal test could not be performed to diagnose dry eye and could not be compared with other authors.

## Conclusion

The main objective of the present study was to determine the association between dry eye disease and influence factors in renal failure patients preparing for kidney transplantation. Previous smoking habits, age, corneal central thickness, conjunctival calcification emerged as reliable predictors of dry eye in renal failure patients. The evidence from this study suggests that eye health care should be taken into account for patients before and after kidney transplantation.

## Abbreviation

TBUT, test break-up time; OSDI, ocular surface disease index; BMI, body mass index; BCVA, best-corrected vision acuity; IOP, intraocular pressure; CCT, central corneal thickness.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. If you have concerns about sharing the data, please contact [nguyenletrungb4@vmmu.edu.vn](mailto:nguyenletrungb4@vmmu.edu.vn).

## Ethical Statements

All participants were dispensed with written informed consents, and the protocol was approved by the Ethical Review Committee of the Hanoi Medical University, Vietnam (Decision no. 467/GCN-HDDDDNCSYHN-DHYHN dated 05/04/2021). All patients provided written informed consent, and that this study was conducted following the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Consent for Publication

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## Disclosure

The authors report no conflicts of interest in this work.

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