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ORIGINAL RESEARCH

Dry Eye and Some Related Factors in Patients with Type 2 Diabetic Nephropathy: A Cross-Sectional Study in Vietnam

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Aim: To determine the prevalence of dry eye (DE) and some related factors in patients with type 2 diabetic nephropathy (T2DN).

Methods: We performed a cross-sectional study on 338 people, who were divided into 2 groups: 169 T2DN patients and 169 patients diagnosed with type 2 diabetic mellitus (T2DM) without renal complications as a control group. The Ocular Surface Disease Index (OSDI) and test fluorescein tear-film break-up time (TBUT) were done in all 338 subjects. Patients with OSDI scores < 13 and TBUT values equal to or under 10 seconds were diagnosed with dry eye.

Results: The prevalence of DE in T2DN patients was significantly higher than T2DM group (55.6% versus 37.3%). The T2DN groups with dry eye had a median duration of DM, the proportion of hypertension, peripheral nerve complications, anemia, proportion of using insulin, and concentration of plasma glucose, HbA1C, urea, creatinine, CRP-hs significantly higher than those of T2DN without dry eye. Advanced age, high HbA1C level, and decreased eGFR were independent factors associated with dry eye in T2DN patients.

Conclusion: Dry eye was a common condition associated with advanced age, high HbA1C levels, and decreased GFR in T2DN patients.

Keywords: type 2 diabetic nephropathy, dry eye, glomerular filtration rate, hemoglobin A1C

Introduction

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[1] Dry eye is a relatively common condition with a global prevalence ranging from 20% to 50%, depending on the evaluation criteria with symptoms, signs alone or in combination.[2] Dry eyes negatively affect vision and quality of life.[3–5]

Diabetes mellitus is one of the most common metabolic diseases in the world. As of 2021, there will be 537 million people with diabetes worldwide. This number is expected to increase to 643 million people in 2030 and 783 million people in 2045.[6] Kidney complications and eye complications are common in diabetic patients. Eye complications, including dry eyes, are an early complication in patients with type 2 diabetes mellitus (T2DM). The prevalence of dry eyes in T2DM patients also ranges from 15% to 53%.[7–10] The pathogenesis of dry eye caused by type 2 diabetes is mainly related to peripheral corneal neuropathy, tear film instability, ocular surface inflammation, and the apoptosis of conjunctival epithelial cells.[11] Another mechanism involved is that with prolonged hyperglycemia, tear osmolarity

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increases, while conjunctival mucus secretion is significantly reduced, leading to decreased tear secretion and increased tear film instability.[12,13]

In fact, kidney complications and eye complications often go together, and "renal-retinal syndrome" originates from this coincidence.[14] There have been many studies on dry eyes in diabetic patients. However, the prevalence of dry eyes and related factors in patients with type 2 diabetic nephropathy has not been studied much. We conducted this study to investigate the association between dry eye and renal complications in T2DM patients.

Patients and Methods

Patients

A total of 245 patients diagnosed with type 2 diabetic nephropathy (T2DN) were monitored and treated at Nghe An Friendship General Hospital, Nghe An province, Vietnam, from January 2022 to January 2023. Patients were diagnosed with diabetic nephropathy (DN) as had one in 3 following criteria: positive microalbuminuria; macroalbuminuria; estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 equal or more than 3 months. We excluded patients with ophthalmological inflammatory complications, contact lens users, prior eye surgery, or those taking medications associated with dryness. Patients on hemodialysis; acute infection; suspected surgical disease; pregnant or lactating women were also excluded from this study. The remaining 169 patients who met the criteria wrote a written informed consent to participate in this study voluntarily. We also used 169 patients diagnosed with type 2 diabetic mellitus (T2DM), without renal complications, as the control group to participate in this study. We collected all data on clinical characteristics and laboratory parameters at the baseline time of the study.

The Ocular Surface Disease Index (OSDI) and fluorescein tear-film break-up time (TBUT) were done on a total of 338 patients according to standard recommendations.[15,16] The above two indexes were performed by ophthalmologists at the Nghe An Eye Hospital. OSDI is a 12-item questionnaire that scores the dryness symptoms on a scale from 0 to 100. Patients with values of 0–12 are considered normal, from 13 to 22 with light, from 23 to 32 with moderate, and values >32 (33–100) with severe symptoms.[15] TBUT was measured for each eye 3 times, and the TBUT value of the measured eye was the average of the 3 measurements. Fluorescein staining and TBUT measurements will be repeated in the remaining eye. For statistical purposes, the TBUT value was the worst result from both eyes. Patients with TBUT values equal to or under 10 seconds in at least one eye are determined to have dry eye.[16]

Disease duration, blood pressure, peripheral nerve complications, treatment data, hematological and biochemical indexes such as urea, creatinine, albumin, protein, high sensitive C-reactive protein (CRP-hs) as well as fasting glycemia and HbA1c were collected simultaneously with the Schirmer test. Lipid disorder was confirmed by testing lipid parameters when there was one or more disorders such as blood cholesterol > 5.2 mmol/L (200 mg/dL); triglycerides > 1.7 mmol/L (150 mg/dL); LDL-cholesterol > 2.58 mmol/L (100 mg/dL) and/or HDL-cholesterol < 1.03 mmol/L (40 mg/dL).

Statistical Analyses

All the normal distribution continuous data were represented by mean and standard deviation and were analyzed using the Student's *t*-test. The skewed distributions were described by median (25 percentile – 75 percentile) and analyzed using the Mann Whitney U and Kruskal Wallis tests. Categorical data were presented by the frequency and were analyzed using the Chi-square test. Multivariable adjusted regression analysis was performed to identify the independent factors related to dry eye. Statistical analysis was performed using Statistical Package for Social Science (SPSS) version 20.0 (Chicago, IL, USA) with a p-value <0.05 was considered significant.

Results

Table 1 shows the T2DN group had mean age, the median duration of DM, the proportion of hypertension, peripheral nerve complications, anemia, lipid disorder, plasma urea, creatinine, CRP-hs, the proportion of using insulin higher than those of T2DM, p< 0.01, 0.001. The T2DN group's OSDI score was higher, but the TBUT was significantly lower than the T2DM group, p<0.001. The prevalence of dry eyes in the T2DN group was significantly higher than in the T2DM group, p < 0.001.

Table 1 Comparison of Demographic and Laboratory Characteristics in Group 1 and Group 2

Clinical Characteristics and Laboratory Parameters	Total (n=338)	Group T2DN (n=169)	Group T2DM (n=169)	p
Ages (Years), ($\bar{X}$± SD)	64.19 ± 10.21	66.47 ± 9.4	61.91 ± 10.51	*< 0.001*
Sex Male (n,%) Female (n,%)	 163 (48.2) 175 (51.8)	 83 (49.1) 86 (50.9)	 80 (47.3) 89 (52.7)	 0.744
Duration of DM, Median (IQR)	10 (5–14)	11 (8–17)	8 (4–10)	*< 0.001*
BMI (kg/m^2) < 18.5 18.5–22.9 ≥ 23.0 ($\bar{X}$± SD)	 30 (8.9) 148 (43.8) 160 (47.3) 22.92 ± 3.36	 13 (7.7) 75 (44.4) 81 (47.9) 22.95 ± 3.26	 17 (10.1) 73 (43.2) 79 (46.7) 22.89 ± 3.46	 0.746 0.866
BP - Systolic BP, ($\bar{X}$± SD) - Diastolic BP, ($\bar{X}$± SD) - Hypertension (n,%)	 133.21 ± 17.87 79.71 ± 8.76 136 (40.2)	 135.54 ± 19.28 80.87 ± 8.85 82 (48.5)	 130.87 ± 16.07 78.55 ± 8.53 54 (32)	 *0.016* *0.015* *0.002*
Peripheral nerve complications (n,%)	58 (17.2)	45 (26.6)	13 (7.7)	*< 0.001*
Anemia (n,%)	139 (41.1)	86 (50.9)	53 (31.4)	*< 0.001*
Hemoglobin (g/L), ($\bar{X}$± SD)	127.6 ± 15.42	124.91 ± 17.1	130.28 ± 13.04	*0.001*
Hematocrit (L/L), ($\bar{X}$± SD)	0.38 ± 0.05	0.36 ± 0.06	0.39 ± 0.03	*< 0.001*
Plasma protein (g/L), ($\bar{X}$± SD)	68.91 ± 7.14	68.77 ± 6.91	69.06 ± 7.37	0.702
Plasma albumin (g/L), ($\bar{X}$± SD)	37.65 ± 4.33	36.98 ± 4.71	38.31 ± 3.82	*0.005*
Lipid disorder (n,%)	304 (89.9)	160 (94.7)	144 (85.2)	0.004
Glucose (mmol/L) ≥ 7.0 Median (IQR)	 308 (91.1) 12.1 (10–17.4)	 152 (89.9) 11.5 (9.34–16.1)	 156 (92.3) 12.3 (10.2–17.44)	 0.444 0.073
HbA1C (%) ≥ 6.5 Median (IQR)	 321 (95) 9.56 (8–11)	 159 (94.1) 9.32 (7.74–10.7)	 162 (95.9) 9.76 (8.03–11.2)	 0.455 *0.032*
Urea (mmol/L), Median (IQR)	5.94 (4.71–8.5)	6.9 (5.5–9.52)	5.1 (4.28–6.7)	*< 0.001*
Creatinine (µmol/L), Median (IQR)	81.9 (71.4–100.95)	98.8 (77.55–137.8)	77.3 (66.5–84)	*< 0.001*
eGFR (mL/min/1.73m^2) < 60 (n,%) - Median (IQR)	 88 (26) 69.7 (57.72–83.7)	 88 (52.1) 57.9 (40.65–73.4)	 0 (0) 78.9 (69.4–86.8)	 *< 0.001* *< 0.001*
CRP-hs (mg/L), Median (IQR)	1.3 (0.85–2.3)	1.6 (0.9–2.55)	1.2 (0.8–2.1)	*0.002*
Using Insulin (n,%)	141 (41.7)	87 (51.5)	54 (32)	*< 0.001*
OSDI (Scale) Normal (n%) Mild (n,%) Moderate (n,%) Severe (n,%) Median (IQR)	 181 (53.6) 49 (14.5) 30 (8.9) 78 (23.1) 12 (6–31)	 75 (44.4) 21 (12.4) 13 (7.7) 60 (35.5) 16 (8.5–39.5)	 106 (62.7) 28 (16.6) 17 (10.1) 18 (10.7) 10 (6–20.5)	 *< 0.001* *< 0.001*

(*Continued*)

Table 1 (Continued).

Clinical Characteristics and Laboratory Parameters	Total (n=338)	Group T2DN (n=169)	Group T2DM (n=169)	p
TBUT (second), Median (IQR)	13 (8–17)	9 (6–14.5)	14 (8–18)	*< 0.001*
Dry Eye (n,%)	157 (46.4)	94 (55.6)	63 (37.3)	*0.001*

Note: Italic value, significant differences.

Abbreviations: T2DN, Type 2 Diabetic Nephropathy; T2DM, Type 2 Diabetic Mellitus; SD, Standard Deviation; DM, Diabetic Mellitus; IQR, Interquartile Range; BMI, Body Mass Index; BP, Blood Pressure; HbA1C, Hemoglobin A1C; eGFR, estimated Glomerular Filtration Rate; CRP-hs, High Sensitive C-reactive Protein; TBUT, tear-film break-up time; OSDI, Ocular Surface Disease Index.

The results in Table 2 shows that the dry eye group of T2DN had the mean age, median duration of DM, the ratio of females, hypertension, peripheral nerve complications, anemia, glucose, HbA1C, plasma urea, creatinine, CRP-hs, the proportion of using insulin higher than those of T2DN without dry eye, p< 0.05, 0.001. In particular, the T2DN group with dry eyes had a higher OSDI scale, and the TBUT was lower than the T2DN group without dry eyes, p< 0.001.

Based on the multivariate logistic regression model in Table 3, we found that older age, female, high HbA1C, and decreased eGFR were independent factors associated with dry eye in T2DN patients, p< 0.05, 0.001.

Table 2 Comparison of Demographic and Laboratory Characteristics in Patient Diabetic Nephropathy with and without Dry Eye (n=169)

Clinical Characteristics and Laboratory Parameters	Total (n=169)	Dry Eye (n=94)	Non Dry Eye (n=75)	p
Ages (Years), ($\bar{X}$± SD)	66.47 ± 9.4	72.31 ± 7.44	59.14 ± 5.78	*< 0.001*
Sex: Male (n,%) Female (n,%)	 83 (49.1) 86 (50.9)	 38 (40.4) 56 (59.6)	 45 (60) 30 (40)	 *0.011*
Duration of DM, Median (IQR)	11 (8–17)	15 (10–20)	10 (4–15)	*< 0.001*
BMI (kg/m^2) < 18.5 18.5–22.9 ≥ 23.0 ($\bar{X}$± SD)	 13 (7.7) 75 (44.4) 81 (47.9) 22.95 ± 3.26	 8 (8.5) 39 (41.5) 47 (50) 22.62 ± 2.83	 5 (6.7) 36 (48) 34 (45.3) 23.36 ± 3.71	 0.68 0.157
BP - Systolic BP, ($\bar{X}$± SD) - Diastolic BP, ($\bar{X}$± SD) - Hypertension (n,%)	 135.54 ± 19.28 80.87 ± 8.85 82 (48.5)	 135.33 ± 19.83 80.93 ± 8.38 50 (53.2)	 135.81 ± 18.7 80.78 ± 9.46 32 (42.7)	 0.872 0.914 0.174
Peripheral nerve complications (n,%)	45 (26.6)	33 (35.1)	12 (16)	*0.005*
Anemia (n,%)	86 (50.9)	62 (66)	24 (32)	*< 0.001*
Hemoglobin (g/L), ($\bar{X}$± SD)	124.91 ± 17.1	119.29 ± 13.9	131.94 ± 18.19	*< 0.001*
Hematocrit (L/L), ($\bar{x}$± SD)	0.36 ± 0.06	0.35 ± 0.05	0.38 ± 0.06	*0.007*
Plasma protein (g/L), ($\bar{x}$± SD)	68.77 ± 6.91	67.9 ± 6.45	69.85 ± 7.36	0.067
Plasma albumin (g/L), ($\bar{X}$± SD)	36.98 ± 4.71	36.24 ± 4.66	37.92 ± 4.63	*0.021*
Lipid disorder (n,%)	160 (94.7)	89 (94.7)	71 (94.7)	1.000

(*Continued*)

Table 2 (Continued).

Clinical Characteristics and Laboratory Parameters	Total (n=169)	Dry Eye (n=94)	Non Dry Eye (n=75)	p
Glucose (mmol/L) ≥ 7.0 Median (IQR)	 152 (89.9) 11.5 (9.34–16.1)	 90 (95.7) 13.69 (11.17–19.36)	 62 (82.7) 10.06 (7.9–11.6)	 *0.005* *< 0.001*
HbA1C (%) ≥ 6.5 Median (IQR)	 159 (94.1) 9.32 (7.74–10.7)	 94 (100) 10.4 (9.79–11.62)	 65 (86.7) 7.68 (6.91–8.76)	 *< 0.001* *< 0.001*
Urea (mmol/L), Median (IQR)	6.9 (5.5–9.52)	8.08 (5.79–12.62)	6.31 (5.3–8.5)	*0.015*
Creatinine (µmol/L), Median (IQR)	98.8 (77.55–137.8)	104.3 (77.9–168.32)	93.1 (76.5–123.8)	*0.028*
eGFR (mL/min/1.73m^2) < 60 (n,%) - Median (IQR)	 88 (52.1) 57.9 (40.65–73.4)	 56 (59.6) 53.3 (28.07–66.8)	 32 (42.7) 66.4 (51.9–82.8)	 *0.029* *< 0.001*
CRP-hs (mg/L), Median (IQR)	1.6 (0.9–2.55)	2.1 (1.2–3.2)	1.2 (0.7–2.1)	*< 0.001*
Using Insulin (n,%)	87 (51.5)	55 (58.5)	32 (42.7)	*0.041*
OSDI, Median (IQR)	16 (8.5–39.5)	38.5 (23–49)	7 (4–10)	*< 0.001*
TBUT (second), Median (IQR)	9 (6–14.5)	7 (4–9)	15 (14–18)	*< 0.001*

Note: Italic value, significant differences.
Abbreviations: SD, Standard Deviation; DM, Diabetic Mellitus; IQR, Interquartile Range; BMI, Body Mass Index; BP, Blood Pressure; HbA1C, Hemoglobin A1C; eGFR, estimated Glomerular Filtration Rate; CRP-hs, High Sensitive C-reactive Protein; TBUT, tear-film break-up time; OSDI, Ocular Surface Disease Index.

Table 3 Multivariate Logistic Regression Analysis of Some Clinical Variables Related to Dry Eye in Diabetic Nephropathy Patients (n=169)

Variable	OR	95% CI	p
Ages	1.381	1.192–1.600	*< 0.001*
Female	2.211	1.190–4.105	*0.012*
HbA1C	5.951	2.798–12.656	*< 0.001*
Decrease in eGFR	22.182	3.611–136.269	*0.001*

Note: Italic value: significant differences.
Abbreviations: HbA1C, Hemoglobin A1C; eGFR, estimated Glomerular Filtration Rate.

Discussion

Prevalence of Dry Eye in Patients with Type 2 Diabetic Nephropathy

The prevalence of dry eye in T2DN patients was 55.6% (94/169 patients), higher than that of T2DM (37.3% = 63/169 patients), p< 0.001. Many authors worldwide have published the prevalence of dry eyes in T2DM. In 2013, Najafi et al reported a dry eye prevalence of 27.7% in a study performed on 243 patients with type 2 diabetes mellitus.[17] In 2018, in a study on 1360 T2DM, Zho et al found 238 patients, accounting for 17.5% of dry eyes.[18] In 2021, De Freitas et al studied 120 diabetic patients, including 24.1% type 1 DM and 75.8% type 2 DM patients. The study's dry eye prevalence was 38.3%.[9] Recently, in 2023, the study of Mansuri et al on 105 patients with type 2 DM found the dry eye prevalence

was 43.81% (92/210 eyes).[10] Thus, the prevalence of dry eyes in our T2DM patients is similar to that of previous published studies.

The results of our study show that the prevalence of dry eyes in the group of T2DN patients is higher than that of the T2DM group without kidney complications (Table 1). There are no separate studies on dry eye in T2DN patients. However, our results are consistent with the cohort study by Pan et al,[19] which suggested that dry eye increased with a decline in renal function in T2DM patients. In patients with type 2 diabetes, dry eye is associated with several mechanisms, including (1) lacrimal unit dysfunction, (2) abnormal enzyme metabolism and reduced mucus secretion leading to abnormal tear dynamics, (3) lacrimal gland dysfunction due to diabetic neuropathy, and (4) tear film dysfunction.[7] Diabetes-related dry eye is the result of risk factors, including chronic hyperglycemia, diabetic periphery neuropathy, decreased insulin levels, microvasculopathy, and systemic hyperosmotic disturbances.[7,20,21] For T2DN patients, dry eye will increase in incidence and severity due to the effects of chronic kidney disease, especially the decrease in glomerular filtration rate. Recently, dry eye has been considered a disease whose pathogenesis involves metabolic, immunological, and oxidative stress disorders.[22] Dry eye is a common problem associated with inflammation, uremia, and arterial calcification due to impaired calcium-phosphorus metabolism, a common disorder in chronic kidney disease patients, including maintenance hemodialysis.[23,24]

The Relationship Between Dry Eyes and Some Characteristics of Patients with Type 2 Diabetic Nephropathy

To consider factors associated with dry eyes in T2DN patients, we compared the clinical and subclinical indicators between 2 groups of patients with and without dry eyes. The results showed that old age, female gender, increased HbA1C, and decreased GFR were independent factors closely related to dry eye, $p<0.001$ (Tables 2 and 3). Advanced age is a factor associated with dry eyes, which many authors have published in the results of previous studies on both T2DM and renal failure patients.[7–9,24] Aging is associated with several risk factors for dry eye, including changes in ocular surface physiology and neurosensory abnormalities.[25] An association between dry eye and HbA1C has been reported in several studies in T2DM patients.[7,17,19] High HbA1C level represents chronic hyperglycemia, which increases tear glucose levels, leading to hyperosmolarity, a risk factor for dry eye.[26] In addition, hyperglycemia initiates an inflammatory cascade that generates innate and adaptive immune responses in the lacrimal function unit.[7] Besides the characteristics of T2DM patients, the features of renal complications also increase the prevalence and severity of dry eye. Reduced glomerular filtration rate in patients with T2DN causes accumulation of urea toxins, from which organ disorders appear, including hypertension, anemia, chronic inflammation, calcium-phosphorus disorders, and immune response. These are risk factors for increased microvascular damage and secretion disorders, which damage the ocular surface and cause dry eyes.[14,23,24]

Although the research goal has been achieved, our study still has some limitations because it has not fully analyzed the relationship between dry eyes and related factors in T2DN patients.

Conclusion

Dry eye was common in T2DN patients, accounting for 55.6% (94/169 patients). Factors associated with dry eye include advanced age, prolonged disease duration, anemia, decreased plasma albumin, increased HbA1C, increased CRP-hs level, and decreased GFR, in which advanced age, increased HbA1C, and decreased GFR were independently associated factors.

Human and Animal Rights

Animals did not participate in this research. All human research procedures followed the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Ethics Approval and Consent to Participate

This study was approved by the Ethical Committee of Nghe An Eye Hospital (No.0789/QĐ-BVMNA).

Consent for Publication

Informed consent was obtained from all the participants.

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Disclosure

The authors declare no conflicts of interest in this work.

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