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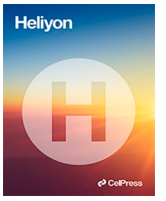

Research article

Measurement of lacrimal gland tissue stiffness for the diagnosis of visual display terminal-associated dry eye disease using shear wave elastography

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ABSTRACT

Objective: This study aimed to evaluate whether lacrimal gland tissue stiffness can aid in diagnosing dry eye disease (DED) using shear wave elastography (SWE). We also aimed to assess the correlation between the subjective symptoms of ocular strain, SWE values, and other ocular examination findings (Schirmer's test and tear film breakup time [TBUT]) contributing to the diagnosis of DED.

Methods: This cross-sectional study recruited 300 participants who were engaged in video display terminal (VDT) work and had been diagnosed with DED by an ophthalmologist for more than one year, and 100 healthy participants without DED symptoms, from August 2020 to December 2021. The modified TFOS DEWS II was used for diagnosing DED. The ocular symptoms, Schirmer's test results, and TBUT of the participants were assessed using standardized methods. Eighty patients with DED and 40 sex- and age-matched healthy participants were selected as the observation and control group, respectively. The lacrimal gland tissue architecture was assessed using ultrasound.

Result: The SWE Emean value reflecting the lacrimal gland tissue stiffness of patients with DED was significantly higher than that of healthy participants (11.06 ± 1.26 for the DED group vs. 7.54 ± 1.27 for the control group, $P < 0.001$). In patients with DED, the Emean values of the lacrimal glands significantly correlated with the scores for subjective symptoms of ocular dryness ($P < 0.001$). No significant correlation was observed between the TBUT and Schirmer's test results. The area under the receiver operating characteristic (ROC) curve for SWE was 0.995. According to the ROC analysis results using an Emean cutoff value of 9.32 kPa for the diagnosis of DED, the sensitivity, specificity, positive predictive value (PPV), and negative predictive (NPV) value were 97.5 %, 95 %, 100 %, and 95 %, respectively. Thus, SWE can be considered for diagnosing VDT-associated DED.

Conclusion: VDT-associated DED was associated with increased tear gland tissue stiffness. SWE aids in the quantitative detection of lacrimal gland tissue stiffness. Moreover, SWE significantly correlated with the subjective symptoms of DED.

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1. Introduction

Dry eye disease (DED), which is a multifactorial disease of the tear film and ocular surface, is caused by decreased lacrimal gland function or rapid evaporation of tears resulting in dryness, which may lead to ocular surface damage. DED is accompanied by increased tear film osmolality and ocular surface inflammation [1]. DED is clinically subdivided into two subtypes: tear deficiency and excessive evaporation. Clinically, mixed forms are commonly observed and often show subjective symptoms and non-specific signs [2], including swelling of the eye, eye pain, dry eyes, itching, blurred vision, foreign body sensation, and tearing. Video display terminal (VDT)-related DED is a type of DED characterized by deficient tear production and excessive evaporation. DED progression could result in extensive scarring of the lacrimal gland tissue, eventually causing decreased ocular accommodation function, destruction and dysfunction of the lacrimal gland acini, and reduced tear production or lacrimal gland microcirculation damage.

With the widespread use of electronic devices and information technology, DED has emerged as a "modern disease." VDT-induced DED, which is a new occupational health problem, has a prevalence of 10 % worldwide [3]. According to an international DED data abstract [4], the prevalence of DED in individuals aged >50 years ranges from 5 % to 30 %. Up to 14–33 % of patients with VDT-associated DED show lacrimal gland involvement [5]. In the United States, 90 % of operators who use computers for more than 3 h a day experience specific symptoms of VDT-associated DED. DED is an inflammatory disease [6]; severe and chronic inflammation can lead to corneal surface damage resulting in the formation of irreparable ulcers or scars, and severe symptoms, such as extreme sensitivity to light, pain, eye redness, and loss of vision [7,8]. Moreover, Kaštelan et al. [5] found that the subjective symptoms of DED may be attributed to chronic inflammation of the lacrimal glands, resulting in lacrimal gland fibrosis, dysfunction, and decreased tear secretion. Therefore, early screening for DED and detection of lacrimal gland fibrosis is necessary for ensuring timely treatment and institution of preventive measures. However, no simple, non-invasive, widely accepted, quantitative method exists for diagnosing DED owing to inadequate sensitivity, specificity and operability of diagnostic tests.

Previous functional testing methods include functional and ultrasound examination of the lacrimal gland, assessment of the ocular symptoms, Schirmer's test, and evaluation of the tear film breakup time (TBUT); however, these methods have certain limitations, such as ocular symptoms indicating severity, Schirmer's test, and TBUT are used to measure the quantity, quality, or functional properties of tears, Schirmer test and TBUT require testing by professional ophthalmologists, and ocular surface symptoms are susceptible to subjective effects.DED results in the loss of lacrimal gland elasticity, which affects its functional and mechanical properties, especially the amount of lacrimal gland fibrosis. Although lacrimal gland biopsy remains the gold standard for histological evaluation of lacrimal gland fibrosis, it is an invasive procedure, which may result in complications, such as damage to the surrounding vital tissues and bleeding. Previously, lacrimal gland evaluation was primarily performed using functional testing rather than imaging methods; thus, a non-invasive, simple, and more accurate diagnostic method is warranted for diagnosing lacrimal gland fibrosis. Thus, increasing interest has been observed in the development of noninvasive methods to quantitatively and accurately assess lacrimal gland lesions and improve the diagnostic capabilities of DED.

High-frequency ultrasound, which is often employed for the initial evaluation of lacrimal gland lesions, is non-invasive, inexpensive, reproducible, and can easily evaluate dynamics in real time.

Shear wave elastography (SWE) is a new ultrasound technology that uses focused sound energy to push pulses of short bursts of sound in real time to generate a vertical main beam of ultrasound waves. Recent studies have demonstrated superior diagnostic performance of SWE when compared to that of lacrimal gland gray-scale ultrasound (LGUS) [2,9,10]. Temporary tissue deformation or displacement occurs when an ultrasound wave passes through the target tissue. An ultrasound scanner can detect tissue displacement and measure the time-to-peak displacement and recovery. Shear wave increases with the velocity of the diseased tissue, which may be significantly stiffer than normal tissue; shear wave is expressed in kilopascals (kPa). Although SWE has been demonstrated as a useful predictor of the severity of interstitial fibrosis and histologic damage [1,11,12], limited literature is available on the loss of lacrimal gland elasticity in VDT-associated DED [13]. This study aimed to assess the involvement of lacrimal gland tissue in VDT-associated DED using LGUS and SWE, and evaluate the association of SWE with ocular fatigue symptoms and other dry eye tests.

2. Methods

2.1. Ethical statement

This study was reviewed and approved by [Medical Ethics Committee of Laibin People's Hospital] with the approval number: [NO 2020-06], dated [August 11, 2020].

2.2. Study design

This cross-sectional study included 80 patients with VDT-associated DED diagnosed using the modified TFOS DEWS II diagnostic assessment method for DED, from August 2020 to December 2021 and 40 healthy participants (matched for age and sex). The inclusion criteria for the patients with VDT-associated DED were: 1) age >18 years; 2) using VDT continuously for more than 3 h per day; 3) history of diagnosis of DED for more than one year by an ophthalmologist, and positive results of the visual fatigue symptom questionnaire scale scores for dry eye, Schirmer's test, and TBUT detection (at least one item was positive).

Exclusion criteria were: 1) presence of ocular organic diseases, such as glaucoma or strabismus; 2) history of eye trauma or surgery; 3) hyperthyroidism, diabetes, hypertension, or other systemic metabolic diseases; 4) anisometropia <1.00 D between the two eyes; 5) lacrimal gland parenchyma thinning (<3 mm); and 6) conditions hindering ultrasound examination of the lacrimal gland.

The inclusion criteria for healthy participants were: 1) age >18 years; 2) individuals in daily occupations involving security and cleaning, or those using VDT <0.5 h per day; and 3) negative results for the visual fatigue symptom questionnaire dry eye scale scores and Schirmer's tests. Participants with common medical conditions, including Sjögren syndrome, ocular inflammation, and those using artificial tears during the study period were excluded from the study.

2.3. Anatomy of the lacrimal gland

The lacrimal gland fossa is located in the bony depression of the superior horn of the outer orbit, which is divided into the orbital and palpebral lobes by the levator palpebral muscle of the upper eyelid; the orbital lobe accounts for approximately 76.6 % of the weight of the lacrimal gland. The size of the lacrimal gland may vary from 20 to 25 mm and 10–14 mm along the long and short axis of the orbit, respectively, and 3–6 mm in thickness [14]. The orbital lacrimal gland is located in the superficial lateral position of the orbit (Figs. 1 and 2); lacrimal gland tissue abnormalities were detected using LGUS and SWE imaging techniques.

2.4. Diagnosis of DED

All the participants were required to provide detailed VDT time and frequency, as well as their clinical history, including ocular signs and symptoms. First, the patient was assessed based on a visual fatigue symptom score questionnaire, followed by evaluation using the Schirmer's test and TBUT examination by an ophthalmologist (LSS, 10 years of experience), and finally by two sonographer (LSS, 10 years of experience; SM, 5 years of experience) for SWE measurement. All the participants provided written informed consent before participation.

2.5. Methods for scoring subjective ocular symptoms

Subjective eye symptoms were included in the diagnosis of DED. The participants filled out the questionnaire according to their condition as follows: 1) name, sex, and age; 2) current continual use of VDT for a long time; 3) current daily cumulative VDT use; and 4) subjective ocular symptom score, which was divided into eyeball swelling, eye pain, dry eye, itching of the eye, blurred vision, diplopia, foreign body sensation, and tearing. The questionnaire scoring criteria [6] were as follows: 0 points, no above-mentioned symptoms; 1 point, occasional occurrence of above-mentioned symptoms, which can be relieved after rest and related to VDT use time; 2 points, frequent occurrence of the above-mentioned symptoms related to VDT use time; 3 points, frequent occurrence of the above-mentioned symptoms with no significant correlation to VDT use time; and 4 points, continuous occurrence of the above-mentioned symptoms, seriously affecting work and life quality, unrelated to VDT use time.

2.6. Schirmer's test

Schirmer's test is widely used for assessing tear volume and lacrimal gland function. In this study, the surface tears were sucked dry from the patient's eye before the test. The patient was asked to look up with the index finger placed at the center of the lower eyelid, pulling the eyelid downwards. One end of the filter paper was folded at 5 mm and placed in the outer third of the conjunctival sac inside the lower eyelid. The rest of the paper was placed perpendicular to the skin surface of the eyelid. The patients were instructed to close their eyes lightly for 5 min. The filter paper was removed and the length wetted by the tears was measured. A value of <5 mm indicated a lack of watery tears.

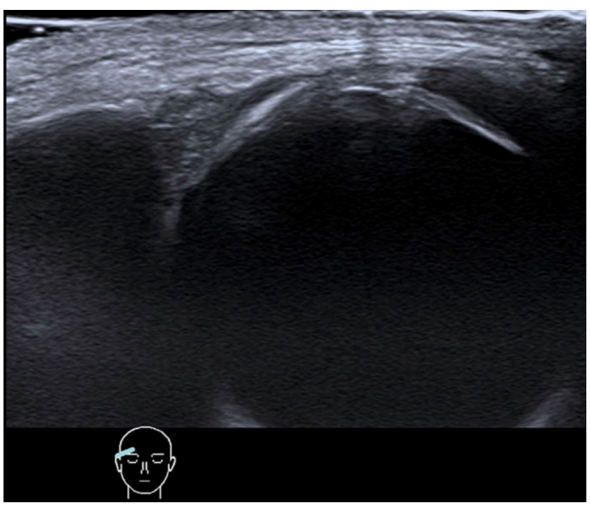

Fig. 1. Subjective visual symptom score value Level 0,LGUS lacrimal gland ultrasonography Level 0.

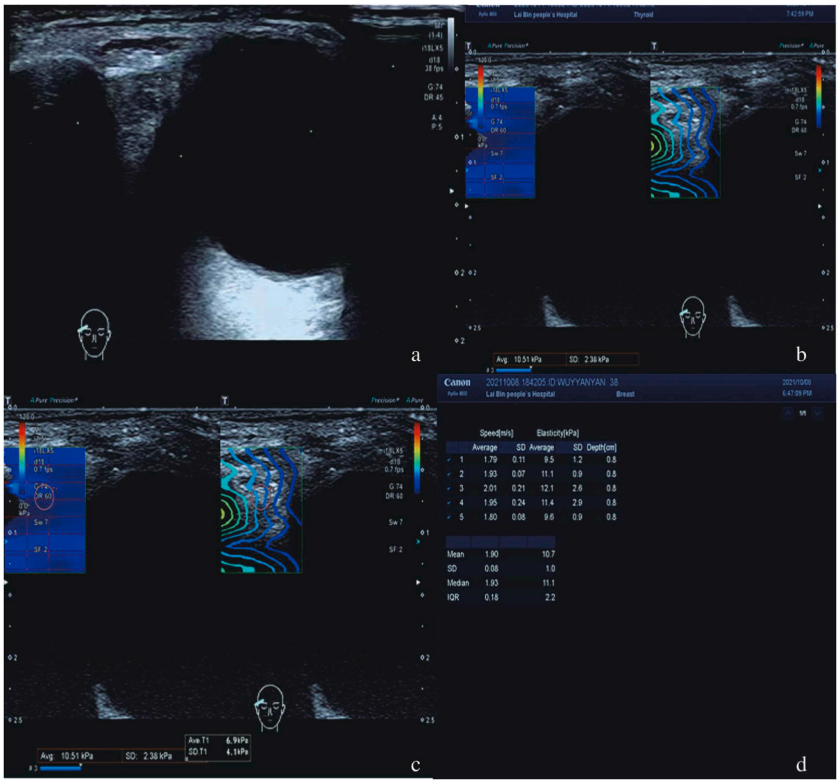

Fig. 2. a Subjective visual symptom score value Level 2,LGUS lacrimal gland ultrasonography Level 2. b The glandular parenchyma area is filled with a color that is complete and stable. c In the SWE mode, the region of interest (ROI) is placed in the center of the sample box for measurement. d Median (median) Young's modulus Emean value of effective stiffness values measured five consecutive times in the right lacrimal gland.

2.7. TBUT

The duration of tear film closure on the eye surface, which represents tear quality, mainly depends on the lipid phase. In this study, the excess tears were suctioned from the eyes of the participants before the examination. The patient's head was placed in a slit-lamp holder with a cobalt blue filter. A drop of 2 % sodium fluorescein was placed under the temporal side of the bulbar conjunctiva; after blinking several times for even distribution of the sodium fluorescein on the cornea, the patients were instructed to open their eyes and stare straight ahead and not blink again. From the time of opening the eyes, the participant's cornea is observed until appearance of the first black spot (tear film defect). The TFBT should be at least 10 s (normal value: 15–30 s) [15–19], the tear film is considered unstable if < 10 s.

3. Ultrasound

3.1. Assessment of the technical features of the ultrasound equipment and SWE

Ultrasound and SWE examination use a color Doppler ultrasound system.

Ultrasound and SWE examinations were performed using an Aplio i800 TUS-AI800 color Doppler ultrasound diagnostic instrument equipped with SWE examination software (Canon Medical Systems Corporation, Japan). The parameters for lacrimal gland evaluation using SWE are as follows: mechanical index <0.23, maximum depth $= 25$ mm, probe frequency $= 18$–24 MHz, axial resolution ≤ 0.5–1 mm,tissue thermal index <1.0, frame rate ≥ 30 fps, gain $= 60$–90, dynamic range $= 55$–70, focus position between 5 and 10 mm, and time gain control was placed in the central position. Each lacrimal gland scan was completed within 5 min.

3.2. LGUS and SWE

The participants were placed in supine position with complete exposure of the examination area and relaxation of the eye muscles. A thick layer of gel was applied over the external surface of the lacrimal gland outside the orbit, and an ultrasound probe (transducer) was placed perpendicular to the skin without exerting pressure on the tissue. Routine ultrasonography of the lacrimal glands was performed for observing the overall size, shape, echogenicity, thickness of the lacrimal glands, and blood flow perfusion, and measuring the systolic peak velocity of the lacrimal gland artery and resistance index. The classification of LGUS was similar to that of

large salivary glands: grade 0 for homogeneous glands; grade 1 for mildly heterogeneous glands compared with adjacent orbital fat tissues showing no hypoechoic areas or diffusely uniform hyperechoic glands; grade 2 for moderately heterogeneous glands showing focal hypoechoic areas within the glands; and grade 3 for diffusely heterogeneous glands displaying low echogenecity throughout the entire gland [20,21].

After evaluating the tear gland tissue, the equipment was switched to the SWE mode and the sampling box was placed in the parenchymal area, where color filling was complete and stable. Blood vessels were avoided and a circular region of interest (ROI) with a size of r = 3 mm was established at the center of the sampling box. The effective stiffness value was measured five times consecutively for each side of the lacrimal gland after obtaining SWE images from at least two different sites of each lacrimal gland. After calculating the median (median) of the five measurements, we defined the interquartile range/median <30 % as a reliable parameter and recorded the mean values of Young's modulus (YM) averaged over both sides of the lacrimal gland in kPa units (Fig. 2). The lacrimal gland tissue stiffness was evaluated using SWE.

3.3. Intra and inter-observer reliability

Intra- and inter-observer reliability studies were performed for the SWE imaging YM measurements. Hardness values were measured five times in the middle of the lacrimal gland and the average value was recorded. For inter-observer reliability, SWE imaging was performed by the first sonographer (LSS, 10 years of experience) and then repeated on the same day by the second sonographer (SM, 5 years of experience). Before conducting this study, the two sonographers received standardized elastography operation training and were familiarized with the operation process of the instrument to ensure that they could independently operate the instrument after evaluation by senior physicians. Ultrasound examinations were performed in a double-blinded manner by the two sonographers. When the SWE imaging measurements of the two sonographers were inconsistent, and after two days, subjects were scanned again to avoid recall bias.

3.4. Statistical analysis

Statistical analyses were performed using SPSS 27.0 (IBM Corp., Armonk, New York, USA). Descriptive statistical analysis was used to compare the demographic characteristics and risk of developing DED between the two groups. Categorical data are expressed as absolute numbers and percentages. The chi-squared test was used to compare the categorical variables. Scatter plots and analyses (Shapiro–Wilk or ANOVA) were used to assess whether continuous variables were normally distributed. According to normal distribution, the continuous variables of each group were compared using the *t*-test alone, and a pairwise *t*-test was used for two-means comparison. Spearman's and Spearman's rho test correlation analyses were used ($P < 0.05$). Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive ability of lacrimal gland SWE imaging results as a criterion for DED. The optimal cutoff value for predicting the Emean value in the observation group (to maximize the sum of sensitivity and specificity) was selected, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The collected data were statistically evaluated, and $P < 0.05$ was considered significant.

The intraclass correlation coefficient (ICC) was used to evaluate the reliability of the Emean measurements for SWE imaging using a two-way random model and an absolute agreement test. The degree of consistency was judged as poor (ICC<0.40), fair to good (ICC 0.40–0.75), and excellent (>0.75).

Table 1
Demographic characteristics of patients and controls.

Variables	DED group (n = 80)	Control group (n = 40)	χ^2/t	P
Course of disease ($\bar{x}$ ±sd, years)	4.33 ± 1.91	–		
Age ($\bar{x}$ ±sd, years)	44.78 ± 16.171	44.08 ± 14.11	0.233	0.816
Female/male	37/43	24/16	1.420	0.159
Emean (kPa)	11.06 ± 1.26	7.54 ± 1.27	14.379	<0.001[a]
Schirmer Test(mm)	6.09 ± 3.02	11.00 ± 1.52	−9.678	<0.001[a]
TBUT	6.19 ± 3.432	16.13 ± 2.172	−11.851	<0.001[a]
Dry eye sign, n (%)	75 (93.75)	5 (12.3)	5.241	<0.001[a]
Lacrimal artery PSV (m/s)	11.89 ± 3.495	12.76 ± 4.15	−1.222	0.225
Lacrimal artery RI resistance index	0.64 ± 0.06	0.67 ± 0.06	−2.660	0.009
LGUS lacrimal gland ultrasonography				
Level 0	9.77 ± 0.44(n = 14)	7.13 ± 1.28(n = 24)	7.390	<0.001[a]
Level 1	11.04 ± 0.98(n = 51)	8.13 ± 1.04(n = 16)	10.184	<0.001[a]
Level 2	11.98 ± 1.23(n = 11)			
Level 3	13.15 ± 1.68(n = 4)			

DED: dry eye disease; PSV,:peak systolic velocity; RI: resistance index.
Note.
[a] : the difference was significant.

4. Results

4.1. General information

A total of 80 VDT operators were included in the DED group, including 37 males and 43 females, with a mean age of 44.78 ± 16.17 years, a history of DED of 1–10 years, and a mean history of 4.33 ± 1.91 years. A total of 40 participants were included in the healthy controls group, including 24 males and 16 females, with an average age of 44.08 ± 14.11 years. No significant differences were observed in the age or sex between the two groups (both $P > 0.05$). The mean Emean values and dry eye symptom scores in the patients with DED were significantly higher than those in the control group ($P < 0.001$), and the Schirmer's test and TBUT scores were lower than those in the control group ($P < 0.001$) (Table 1).We analyzed the Emean values determined by SWE and found that the higher the Emean value was, the more serious the loss of tear gland elasticity. Therefore, dry eye has tissue involvement with lacrimal glands, and SWE can be used to assess TS.

4.2. Lacrimal gland stiffness measurement using SWE and ultrasound

There were significant associations between the mean value of Es in lacrimal glands and subjective symptoms, TBUT and and Schirmer test of DED ($P < 0.001$) (Fig. 3, Table 3, Table 4). No significant correlation was observed between the TBUT and Schirmer's test results. A weak and insignificant correlation was observed between the peak systolic velocity and resistive index of the lacrimal artery in healthy individuals and those with DED ($P > 0.05$) (Table 1). However, statistically significant differences were observed between the one-way analysis of variance Emean values and ocular symptom scores ($F = 41.887$, $P < 0.001$; Table 2).

No significant difference was observed in the elastography findings between the subgroups of the patients with DED with and without ocular fatigue, as confirmed by the Schirmer's test and TBUT evaluation. The SWE values increased among patients with VDT-associated DED upon increase in the visual fatigue symptom scores. However, owing to the small subgroup sizes, the testing ability was low. Table 4 presents the results of lacrimal gland stiffness in patients with DED based on the Schirmer's test and ocular subjective symptom outcomes.

The Emean value of the patients with DED was significantly higher than that of the control group ($P < 0.001$) (Table 1). SWE was able to detect tear gland involvement in patients with VDT-associated DED (Fig. 4). When the cut-off value of visual fatigue symptom score was 1, the area under the ROC curve (AUC) for SWE Emean values of the left and right lacrimal glands was 0.995. According to the results of the ROC analysis, the Emean cut-off value of 9.32 kPa was used to diagnose DED; its sensitivity, specificity, PPV, and NPV were 97.5 %, 95 %, 100 %, and 95 % respectively. When the cutoff value of visual fatigue symptoms was greater than or equal to 2, the AUC of for Emean was 1, the sensitivity, specificity, PPV, and NPV were significantly increased,at 100 %, 100 %, 100 %, and 100 %.The study showed that SWE was significantly associated with subjective symptoms of dry eye, but ocular surface symptoms and signs were not significantly associated with dry eye.

The parenchymal grades of LGUS were 0/14 (17.5 %), 1/51 (63.75 %), 2/11 (13.75 %), and 3/4 (5 %). The LGUS parenchymal grade was 0 (60.0 %) in 24 patients and 1 (40.0 %) in 16 patients (Fig. 2). Among the patients with DED with parenchymal abnormalities of the LGUS (grade ≥1), the Emean value of the patients with DED was higher than that of the control group (grade 0, $P < 0.005$; grade 1, $P < 0.001$).Results showed that SWE was superior to LGUS in diagnosing suspected dry eye disease (Table 1).

4.3. Reproducibility of the YM measurements

We assessed the intra-group correlation coefficient of the diagnostic test repeatability evaluation based on the estimated results of the single measures. The ICC was 0.762 (95 % CI , 0.653–0.841)($P < 0.001$), indicating that the YM measurement had good inter-observer reliability and wide intraobserver reliability.

5. Discussion

In this study, LGUS and SWE were used to evaluate lacrimal gland tissue stiffness in patients with VDT-associated DED, which can be used to distinguish eyes with DED from healthy eyes. Although the subjective symptoms of visual fatigue and SWE values were significant correlation. Moreover, significant correlation was observed between the eye examination, including TBUT evaluation and Schirmer's test, and the diagnosis of DED.

SWE is a new diagnostic tool that objectively quantifies tissue stiffness without using external compression. SWE permits real-time

Table 2
Normal test of SWE's mean of Young's Modulus (Emean) for measuring lacrimal gland stiffness was as follows and ANOVA.

	Normal test				ANOVA	
	Kolmogorov Smirnoff		Shapiro Wilke		F	significance
YM(kPa)	Statistical	Significance	Statistical	Significance		
Subjective visual symptom score value	0.0137	0.001	0.938	0.001	41.887	0.000[a]

Note.
[a] : the difference was significant.

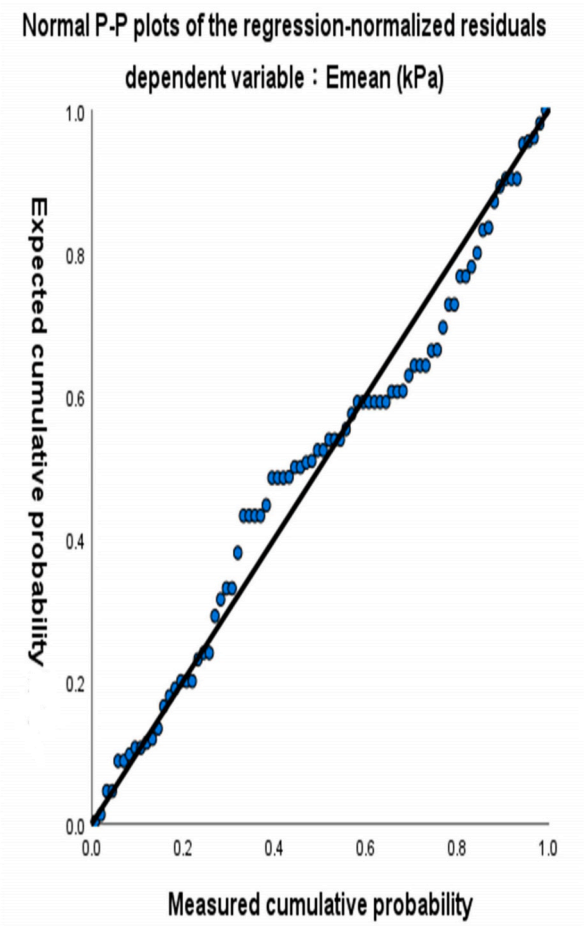

Fig. 3. Emean values and the subjective ocular symptom score in the case group.

Table 3
SWE measures the correlation between different symptom scores for patients with dry eye syndrome and tear gland Emean (kPa).

Subjective visual symptom score value	Emean (kPa)	cut-off value	Sensitivity,%	pecificity,%	P value	AUC,%	PPV,%	NPV,%
1	9.69 ± 0.40	8.94	100	87.5	0.001[b]	97.4(0.938–1.000)[a]	86	100
2	10.96 ± 0.56	9.76	100	100	0.000[b]	100(1.000–1.000)*	100	100
3	12.13 ± 1.22	9.81	100	100	0.000[b]	100(1.000–1.000)[a]	100	100
4	13.9 ± 0.58	11.40	100	100	0.000[b]	100(1.000–1.000)[a]	100	100

Subjective visual symptom score value:Tested in at least one eye of <5 mm/5 min.
[a] The value in parentheses is the 95 % confidence interval. Mark.
[b] : significant difference.

superimposition of color quantitative elastogram on a grayscale image [22], and has recently been increasingly used to assess tissue elasticity loss.

Recent prospective studies [2,9,10] have demonstrated good diagnostic performance of SWE for patients of primary Sjögren's syndrome with lacrimal gland involvement; the AUC, sensitivity, and specificity were 0.898–0.94, 70.6–94 %, and 87–97.6 %, respectively. However, our study used the SWE-derived YM mean (Emean) to quantitatively evaluate the correlation of patients with VDT-associated DED and lacrimal gland involvement. The results demonstrated greater lacrimal gland tissue stiffness. The AUC, sensitivity, specificity, PPV, and NPV were 0.995, 97.5 %, 95 %, 100 %, and 95 %, respectively. No correlation was observed between SWE and age or sex. Özer H et al. [21] studied the AUC value of parotid modulus of elasticity (kPa) (0.937; 95 % CI, 0.901–0.973), with sensitivity and specificity of 93.2 % and 83.3 %, respectively.SWE demonstrated good diagnostic performance for the classification of DED.

Our study demonstrated that the lacrimal gland tissue stiffness levels were significantly higher in patients with DED than in healthy participants. The median Emean (kPa) was 11.06 ± 1.26 for the DED group and 7.54 ± 1.27 for the healthy group, with no significant

Table 4
Comparison of shear wave elastography results inVideo terminal-related dry eye disease with normal and abnormal results of the Schirmer test and TBUT, as well as those with and without subjective eye dryness.

Variable, kPa	Schirmer test<5mm/5min in at least 1 eye (n = 58)	Normal Schirmer test result (n = 22)	P value
Mean SWE values for left and right lacrimal gland(kPa)	11.35 ± 1.26	10.26 ± 0.82	<0.001[a]
	TBUT≤10s at least one eye(n = 57)	Normal TBUT (n = 23)	P value
Mean SWE values for left and right lacrimal glands(kPa)	11.37 ± 1.26	10.27 ± 0.38	<0.001[a]
	TBUT≤10s at least one eye OR Schirmer test<5mm/5min in at least 1 eye (n = 62)	Normal TBUT AND normal Schirmer test result (n = 18)	P value
Mean SWE values for left and right lacrimal glands (kPa)	11.29 ± 1.25	10.23 ± 0.88	0.001[a]
	Subjective eye drynes(n = 26)	No subjective eye drynes(n = 18)	P value
Mean SWE values for left and right lacrimal glands (kPa)	11.14 ± 1.24	9.76 ± 0.32	016

Mark.
[a] : significant difference.

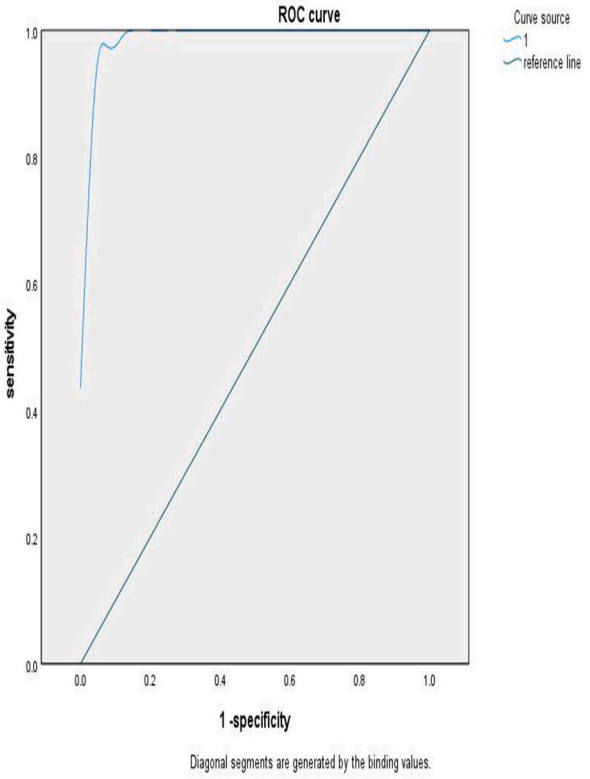

Fig. 4. Receiver operating characteristic (ROC) curve analyses for lacrimal elastography.

correlation with age or sex. According to Özer et al. [20], the average two dimensional-SWE value for patients with primary Sjögren's syndrome was 12.58 ± 3.61 kPa while that of healthy participants was 7.42 ± 1.81 kPa, both showing no correlation with age. However, Cerit et al. [23]. found that the average tissue hardness of healthy participants was 6.17 ± 2.94 kPa using a two-dimensional-SWE method and that age negatively correlated with lacrimal gland tissue stiffness. In their study of healthy participants, Badarinza et al. [24]. reported an average two-dimensional-SWE value of 9.47 ± 2.1 kPa for the lacrimal gland with no significant correlation between age and the SWE values, which could be attributed to the heterogeneity among the research participants, different software used to measure SWE, and variations in operator experience.

Other functional tests for dry eye (Schirmer's test and TBUT evaluation) confirmed moderate difference in the elasticity imaging values between patients with DED with or without ocular fatigue symptoms in our study. Although the results were positive, no

significant correlation was observed. No significant difference was observed between the Emean values of the LGUS and tissue YM with age or symptom duration compared with the Schirmer's test and TBUT; however, significant correlations were observed between Emean and symptoms of visual fatigue, as reported by Hofauer et al. [25]. Although, some studies demonstrated a correlation between ultrasonography findings and Schirmer's test results, Özer et al. [26]. demonstrated no significant correlation between the Schirmer's test results and SWE-related parameters in patients with DED. Świecka et al. [2]. also demonstrated no significant correlation between the intra-group values of the Schirmer's test in patients with DED, which could be attributed to the good specificity and poor sensitivity of Schirmer's test in the assessment of the functional integrity of lacrimal glands [27,28]. Moreover, DED is a multifactorial disease of the tear film and ocular surface with poor correlation between symptoms and signs [29]. Therefore, our study suggests that although elasticity imaging of the lacrimal gland can be used to diagnose VDT-associated DED, objective symptoms cannot indicate disease severity.

In this study, the YM measurement (Emean) of SWE was significant positive correlated with the ocular surface symptom score, and Emean was Significant negatively correlated with TBUT.These findings are consistent with the pathological characteristics of DED. With DED progression, patients demonstrate higher tear gland firmness, which is consistent with the findings of Zhao et al. [2,9,10]. High SWE values in patients with DED indicate chronic inflammatory cell infiltration, destruction of the adenoid tissue, progressive atrophy and fibrosis of the lacrimal gland acinar cells, and reduction of tear secretion [30]. These features indicate that lacrimal gland tissue stiffness positively correlates with the ocular symptoms, which is consistent with the results of this study and with the histological basis of the application of SWE in DED [31]. Increased fibrosis increased the lacrimal gland tissue stiffness scores and accelerated transverse wave propagation, indicating that the degree of salivary gland fibrosis was directly related to transverse wave propagation. This finding is consistent with that of Liu et al. [32], suggesting a significant correlation of Emean with the DED questionnaire symptoms.

LGUS can provide information on the changes within the lacrimal gland parenchyma, such as parenchymal homogeneous blood flow; however, it is subjective and based on the operator, equipment, and methods used. Moreover, conflicting views exist on whether parenchymal heterogeneity solely is sufficient for the diagnosis or whether integration with other characteristic measures, such as parenchymal echogenicity, posterior edge visibility, glandular contour loss, presence of intraglandular lymph nodes, and vascularization, is necessary. Świecka et al. [2]. recently reported that SWE can provide a noninvasive assessment of tissue elasticity or stiffness, thus providing additional information about tissue characteristics and compensating for the limitations of LGUS in the diagnosis of DED and other diseases.

These results show that the average value (Emean) of LGUS and SWE tissue YM can be used to evaluate lacrimal gland tissue stiffness in patients with VDT-associated DED [33], which can be used to distinguish healthy people from DED patient groups.

According to Yang et al. [34], VDT can lead to high resistance and low perfusion of the ophthalmic artery, thus affecting tear secretion, which is similar to the results of the present study. however, no significant correlation between the peak speed of lacrimal artery contraction velocity and resistance index in patients with DED and general health.Thus, this finding is related to the morphological and structural changes in the lacrimal gland and the relationship between the peak systolic velocity and resistive index of the lacrimal gland artery in DED.

5.1. Limitations of the study

Our study had several limitations. First, it is a novel single-center study with relatively small sample size but preliminary results are worth affirming. However, future studies should be carried out in more sample models. Second, we did not include patients with dry eye caused by factors or diseases other than VDT, so we could not determine whether the increase in lacrimal gland stiffness was specific for VDT-related dry eye or common characteristics of lacrimal gland involvement disease.Third, owing to the heterogeneity of the lacrimal gland, SWE estimated a higher change of lacrimal gland tissue stiffness in patients with DED than in controls, which may be related to the differences in Emean attributed to fibrosis of the lacrimal gland. Fourth, since there is no indication for lacrimal gland biopsy in patients with DED-related lacrimal gland disease, there are no biopsy data on the histological quantification of lacrimal gland disease. Finally, since there is no indication for lacrimal gland biopsy in patients with DED-related lacrimal gland disease, there are no biopsy data on the histological quantification of lacrimal gland disease. In this disease-related study, ocular elasticity imaging can be used to explain the application of this imaging technique in the diagnosis of VDT-related dry eye.

6. Conclusions

Our study demonstrated the superiority of SWE to traditional ultrasound for diagnosing DED. We used a critical value of 9.32 kPa to distinguish between patients with DED and healthy participants. Despite its limitations, the estimated lacrimal gland tissue stiffness derived from SWE is an effective, simple, and noninvasive method for providing additional diagnostic information for DED. Moreover, SWE parameters were closely related to the severity of DED.These results are worth further in-depth research into the future, which can finally solve the limitations of the above research. With the quantitative diagnostic efficacy of SWE imaging technology gradually being proved, it is necessary to expand the study object and carry out more extensive studies to establish an Emean value of lacrimal gland stiffness for simple, noninvasive diagnosis of patients with dry eye disease. The prospect of future research may be very prominent.

Abbreviation

Abbreviation	Full name
SWE	Shear wave elastography
DED	Dry eye disease
VDT	Visual display terminal
ROI	Region of interest
TS	Tissue stiffness
AUC	Area under the curve
kPa	kiloPascal
YM	Young's modulus
Emean	Mean values of elasticity
TBUT	Tear breakup time
PSV	Peak systolic velocity

Disclosure statement

The authors did not report any potential conflicts of interest.

Ethics statement

This study was reviewed and approved by [Medical Ethics Committee of Laibin People's Hospital] with the approval number: [NO 2020-06], dated [August 11, 2020].

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Availability of data and materials

No data was used for the research described in the article:

CRediT authorship contribution statement

Xianling Mo: Writing – original draft, Data curation, Conceptualization. **Huiyan Meng:** Formal analysis, Data curation. **Yanyan Wu:** Formal analysis, Data curation. **Suqin Yang:** Formal analysis, Data curation. **Yu Zhang:** Formal analysis, Data curation. **Yiqiu Zhou:** Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33912.

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