S Afr Optom 2013 **72**(2) 55-60

Tear osmolarity and OSDI symptoms: is there a relationship?

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Received 21 January 2013; revised version accepted 18 June 2013

Introduction

Dry eye is defined as: "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 ubiquitous disease with estimates of between 5% and 35% prevalence being reported in various research studies[2-6]. The diagnosis of dry eye is difficult, in part due to a paucity of information relating to a standardized set of diagnostic criteria and the absence of a "gold standard"[7] as well as the poor correlation between the symptoms that patients present with and the clinical signs that might be observed[8, 9]. Various studies have shown that only approximately 57% of patients presenting with symptoms of dry eye have objective signs of the disease[9-11]. The use of symptomatology (determined using validated symptom questionnaires) in the diagnosis of dry eye disease presents an important and accessible diagnostic tool to clinicians and researchers of dry eye[7]. The diagnostic subcommittee of the International Dry Eye Workshop have stated: "…the administration of a structured questionnaire to patients presenting to a clinic provides an excellent opportunity for screening patients with potential dry eye disease"[7]. Questionnaires are commonly used to investigate the prevalence of dry eye in various sample groups, in screening for dry eye, to investigate the effects of different dry eye treatment strategies and to grade the severity of dry eye disease states[12-19]. It has also been suggested that questionnaires might be more valuable in diagnosing dry eye than dry eye tests[13]. The outcomes research group at Allergan Incorporated (Irvine, California) developed a 12-item questionnaire, the Ocular Surface Disease Index (OSDI), to…"provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning"[20]. The validity and reliability of the OSDI were evaluated by Schiffman *et al*[21] who found the OSDI to be a reliable and valid instrument for determining the severity of dry eye disease. Ozcura *et al*[22] also found the OSDI to be a standardized test for the evaluation of symptoms of dry eye and that the instrument can be used to support the diagnosis of dry eye disease. Dougherty *et al*[23] , however, show that the OSDI "is not ideally targeted for patients with dry eye disease".

Osmolarity is a measure of the concentration of a solute and is defined[24] as the number of osmoles of solute per litre of solution (Osm/l). The process of osmometry is the measuring of solute concentration and takes into account the dissociation of solutes in solution[25]. A convenient, clinical measurement of tear osmolarity has only recently become a reality with the availability of the TearLab™ osmolarity system. The TearLab™ system …"is a tear fluid collection and testing device for the quantitative measurement of osmolarity of human tears…" that provides… "a quick

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and simple method of determining tear osmolarity using nanolitre volumes of tear fluid collected from the eyelid margin"[26] . The conclusions of several research articles have stated that tear osmolarity is the best single metric to use in the diagnosis and classification of dry eye[8, 27-28]. Sullivan *et al*[29] have stated that tear osmolarity is the best single marker of dry eye disease severity when investigating normal, moderate and severe cases of dry eye. Suzuki *et al*[30] have stated: "Tear osmolarity correlates with dry eye severity and therefore could provide a biomarker for disease severity". Bechtel[31], commenting on a poster prepared and presented at an American Academy of Ophthalmology meeting by Foulks, states that tear osmolarity may function as an accurate diagnostic tool in early dry eye disease. Investigating the variability of osmolarity, over a three month period, in dry eye disease, Sullivan *et al*[32] indicate that osmolarity of the tear film had the lowest variability when compared with other commonly used tests for dry eye disease. Tomlinson *et al*[33] determined a referent of 316 mOsmol/l as a cut-off point for the diagnosis of dry eye. They also stated that "hyperosmolarity (defined as >316 mOsmol/l) was superior in overall accuracy to any other single test for dry eye diagnosis…" Gillan[34] has shown that the TearLab™ system provides reasonably accurate, repeatable and reproducible results when measuring osmolarity of a calibration/test solution. Investigating the repeatability and accuracy of two different instruments, Yildiz *et al*[35] were able to show that osmolarity measurements were repeatable when measuring four different solutions of different osmolarity. The methodology subcommittee of the Dry Eye Workshop[7] has stated that: "Tear hyperosmolarity may reasonably be regarded as the signature feature that characterizes the condition of ocular surface dryness" and that the "…recommended cut-off value of 316 mOsmol/l can be said to be well validated".

If the use of questionnaires does enable one to diagnose dry eye and if osmolarity is the single best metric for determining the presence of dry eye, then it might not be unreasonable to expect some kind of relationship between the two diagnostic methods. The purpose of this study was to investigate whether any relationship exists between the symptoms of dry eye (as determined using the OSDI) and tear osmolarity measured using the TearLab™ osmolarity system.

Method

Forty optometry students (10 of whom were wearing contact lenses) studying at the University of Johannesburg volunteered to participate in this study. All students were aged between 19 and 25 years and gave written informed consent for the investigation. The tenets of the Declaration of Helsinki were adhered to throughout the study. Male and female subjects were included. The TearLab™ osmolarity system was used to measure the tear osmolarity of each subject (for a detailed exposition of how the TearLab™ system works and is used, the reader is referred to the TearLab™ system user manual). Prior to use the measuring pen was calibrated/checked by attaching the electronic check card to the measuring pen and then placed on the reader. The read-out for the electronic check card was within manufacturer specifications. Only the left eye of each subject was measured. Prior to measuring osmolarity a new test card was attached to the reader for each subject. The subject was seated comfortably and asked to "look up and to the right" after which the tip of the test card was gently placed onto the tear meniscus of the lower lid. No attempt was made to pull the lower lid from the eye. An effort was made to not irritate the eye when collecting the tear sample. Once the pen emitted a loud beep (indicating that an adequate sample had been collected) the pen was then docked onto the reading device within 40 seconds (according to manufacturer instructions). A measurement of tear osmolarity was produced by the reading device, which was then recorded. The test card was then removed from the pen and discarded.

Each subject completed the OSDI questionnaire within 24 hours of having tear osmolarity measured. The OSDI score is assessed on a scale of 0 to 100 with higher scores indicting greater disability related to dry eye. The developers of the OSDI provide an OSDI formula which is used to convert the answers on the OSDI questionnaire to an OSDI score[20]. This OSDI score is then used to determine the level of disability related to dry eye. The OSDI formula is:

$$\text{OSDI score} = \frac{(\text{sum of scores}) \times 25}{(\text{number of questions answered})}$$

(Readers interested in acquiring the OSDI and instructions for its use are referred to: dryeyezone.

com where one can search for OSDI or search for OSDI using Google). An OSDI score was calculated for each subject. Statistical analysis was done using Medcalc statistical software for biomedical research.

Results

Table 1 shows the raw data collected in this study. Included in the table are the tear osmolarity for each subject, the OSDI score and whether the subject was wearing contact lenses or not. The mean osmolarity for the 40 subjects was 315.5 ±14.4 mOsmol/l (median: 314.0 mOsmol/l) while the mean OSDI score was 23.5 ±16.6 (median: 16.7 mOsmol/l). Figure 1 shows box and whisker plots for the data collected where the box indicates values from the lower to the upper quartile, the middle line represents the median, the vertical line extends from the lowest to the highest value but excludes values that are considered to be outsider values (Figure 1a shows three data points not included on the vertical line).

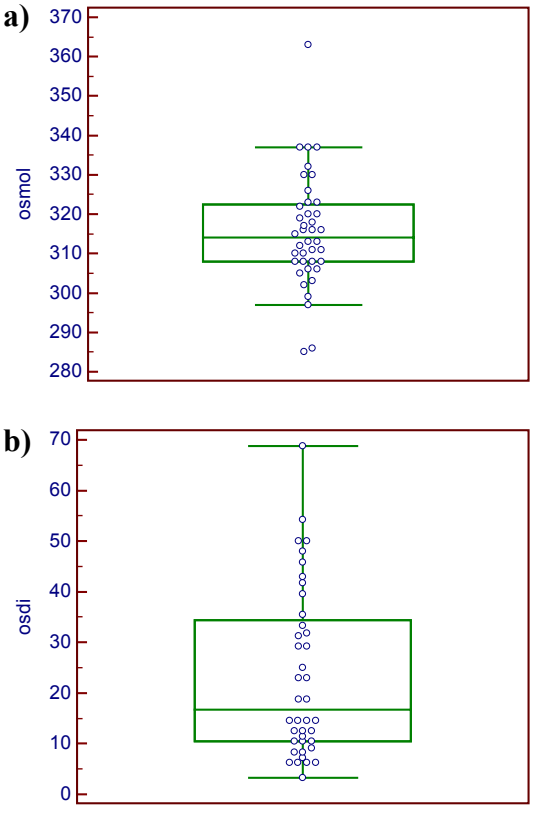

Figure 1. Box and whisker plots of medians and interquartile ranges are shown for tear osmolarity (Figure 1a) and OSDI score (Figure 1b). Circles indicate each measurement/score. See text for an explanation of the plots.

Table 1. Data collected from 40 subjects. Mean osmolarity is 315.5 ± 14.4 mOsmol/l with the median 314.0 mOsmol/l.

Subject	Osmolarity (mOsmol/l)	OSDI score	Contact lens wearer?
1	312	33.3	N
2	311	10.4	N
3	308	11.4	N
4	310	7.3	N
5	317	68.7	N
6	302	12.5	N
7	337	45.8	N
8	326	8.3	Y
9	332	8.3	N
10	320	10.5	Y
11	306	31.8	N
12	303	23.0	N
13	337	47.9	Y
14	297	14.6	N
15	316	39.6	N
16	330	50.0	N
17	316	29.2	N
18	313	54.2	N
19	316	22.9	N
20	310	6.3	N
21	308	18.7	N
22	315	6.3	N
23	319	3.3	N
24	305	35.4	N
25	323	25.0	N
26	313	12.5	N
27	320	14.6	N
28	318	42.9	N
29	323	10.4	N
30	330	31.3	Y
31	363	9.1	N
32	308	18.8	Y
33	311	6.3	N
34	285	6.3	N
35	322	29.2	Y
36	337	50.0	Y
37	308	12.5	N
38	286	14.6	Y
39	306	14.6	Y
40	299	41.7	Y

Figure 2 is a scatter plot of tear osmolarity *versus* OSDI score. Included is the linear regression line (solid blue line) as well as the 95% confidence interval for the regression line (dotted red line). There is no obvious trend to be seen in the data plotted. The regression equation is: $y = 310.96 + 0.191x$. A Kolmogorov-Smirnov test for normal distribution was conducted on each set of data and both sets of data were found to be normally distributed. A correlation coefficient was determined for the tear osmolarity and OSDI score data. A weak, positive, statistically insignificant, correlation between tear osmolarity and OSDI score was found ($r = 0.22$, $p = 0.17$).

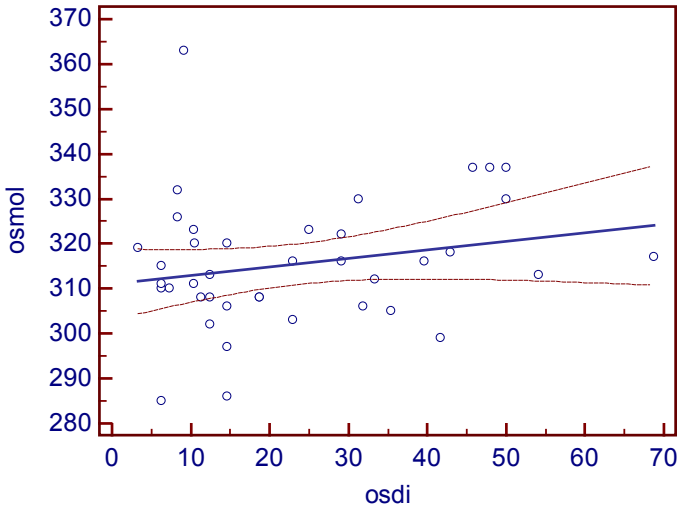

Figure 2. A scatter plot of tear osmolarity (osmol) *versus* OSDI score (osdi) is shown. Included is the linear regression line (solid blue line) with its associated 95% confidence interval (dotted red line), ($r = 0.22$ $p = 0.17$).

A primary reason for contact lens intolerance is ocular dryness[36] with reports that approximately 50% of contact lens wearers experience dry eye symptoms at least on some occasions[37-39]. Young *et al*[40] have shown evidence suggesting that approximately 25% of symptomatic contact lens wearers do not have visible signs of ocular surface disease. The mean tear osmolarity for the 10 contact lens wearers in this sample of subjects was 317.1 ± 16.9 mOsmol/l. The mean OSDI score for the 10 contact lens wearers was 26.6 ± 15.6. A correlation coefficient between tear osmolarity and OSDI score was also determined for the 10 contact lens wearers of this sample. A weak (slightly stronger correlation than that seen when all 40 subjects were included) positive, statistically insignificant correlation between tear osmolarity and OSDI score was determined ($r = 0.45$, $p = 0.20$). Figure 3 shows a scatter plot of the tear osmolarity *versus* OSDI for the ten contact lens wearers.

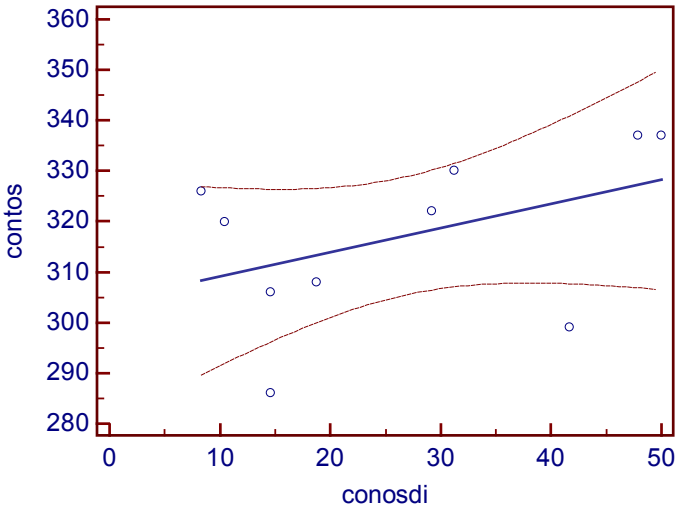

Figure 3. Tear osmolarity (contos) *versus* OSDI score (conosdi) data (for the ten contact lens wearers in this sample) is represented in this scatter plot. Included is the linear regression line (solid blue line) with its associated 95% confidence interval (dotted red line), ($r = 0.45$ $p = 0.20$).

Discussion

The aim of this study was to determine if a relationship exists between the symptoms of dry eye (determined using the OSDI) and tear osmolarity (using the TearLab™ osmolarity system). Using questionnaires to diagnose dry eye is an important tool for clinicians[7] with the suggestion having been made that questionnaires are more valuable in the diagnosis of dry eye than other tests[13]. Osmolarity has been touted as being the best single metric to use when attempting to diagnose dry eye[8, 27-28] with Suzuki *et al*[30] stating that "tear osmolarity correlates with dry eye disease…". Tomlinson *et al*[33] have determined that a cut-off point of 316m Osmol/l should be used when using tear osmolarity for the diagnosis of dry eye.

The correlation between tear osmolarity and OSDI score in this sample of 40 optometry students has been shown to be weak and statistically insignificant. The same conclusion has been shown for the 10 subjects who wore contact lenses. These findings are in agreement with those shown by Dalton[41] who, using

the OSDI, the Single Item Dry Eye Questionnaire (SIDEQ) and the McMonnies Dry Eye Questionnaire (MMDEQ), found no correlation between the symptoms suggested by the questionnaires and tear osmolarity ($r = 0.14$, $r = 0.03$ and $r = 0.27$ for the SIDEQ, OSDI and MMDEQ respectively). Nineteen (47.5%) of the 40 subjects in this study had a tear osmolarity of 316 mOsmol/l or greater and using Tomlinson *et al*[33] referent as a guideline, these 19 subjects could be classified as having dry eyes. However, when evaluating the correlation between tear osmolarity and OSDI score for the 19 subjects in this instance, a poor, negative, statistically insignificant correlation was found ($r = -0.06$, $p = 0.82$). Using an OSDI score of 15 as a cut-off point for symptomatic individuals[21, 42-43], 20 of the 40 (50%) subjects could be considered symptomatic for dry eye. Nevertheless, no relationship between tear osmolarity and OSDI score was found.

In conclusion, little correlation was found between tear osmolarity and OSDI score in the subjects investigated in this study. It is possible that the OSDI is a poor questionnaire for the diagnosis of dry eye (as suggested by Dougherty *et al*[23], the OSDI does not ideally target dry eye disease) yet, as shown by Dalton[41], other dry eye questionnaire results do not correlate with tear osmolarity either. Is the TearLab™ osmolarity system an accurate, repeatable and reproducible instrument to determine tear osmolarity? Several authors suggest that this is the case[28-29, 34]. The question as to how clinicians correctly decide if a patient has dry eye or not still seems to be a difficult one to answer.

Acknowledgements

My thanks to the following students for the collection of the data used in this study: C Meyer, T Miller, T Dangor and W McPherson.

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