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ORIGINAL RESEARCH

Tear osmolarity and dry eye symptoms in diabetics

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Purpose: To assess the relationship between tear osmolarity and dry eye symptoms in patients with diabetes.

Patients and methods: Fifty patients with diabetes were enrolled. Demographic information and past medical history were recorded. Symptoms were assessed using the ocular surface disease index (OSDI). Tear osmolarity of each eye was measured with the TearLab® Osmolarity System.

Results: The majority of the subjects were female (76%), African American (56%), and/or had a diagnosis of type 2 diabetes (82%). The mean ± standard deviation (SD) for age was 54.6±13.4, and maximum tear osmolarity was 304.6±12.7 mOsm/L. Men had higher osmolarity than women (mean ± standard error (SE) 311.8±4.0 mOsm/L versus 302.3±1.9 mOsm/L, P=0.02). Age, race, use of artificial tears, years of diabetes, and hemoglobin A1c did not have a statistically significant association with tear osmolarity. Longer duration of diabetes was associated with lower (less severe) OSDI scores (r=–0.35, P=0.01). Higher tear osmolarity was associated with lower (less severe) OSDI scores (r=–0.29, P=0.04).

Conclusion: Approximately half of the diabetic subjects in our study had elevated tear osmolarity, and half of our population also reported symptoms consistent with dry eye disease. However, the two were slightly inversely related in that those with higher osmolarity reported fewer symptoms. Subjects with a longer duration of diabetes also reported fewer dry eye symptoms. Therefore, health care providers should be aware that patients who are most likely to have ocular surface disease, including those with long-standing diabetes, may not experience symptoms and seek care in a timely manner.

Keywords: dry eye, osmolarity, diabetes

Introduction

In 2007, the Dry Eye Workshop (DEWS) defined dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[1] Dry eye disease (DED) is common and significantly affects quality of life. The estimated prevalence of DED for women and men over the age of 50 years in the United States is 3.2 million and 1.6 million, respectively.[2,3] Compared with age-matched controls, patients with dry eye are two to four times more likely to experience difficulty with reading, carrying out professional work, using a computer, watching television, and driving.[4]

The assessment of tear film osmolarity may be helpful in the study of DED, as tear osmolarity changes have been shown to reflect disturbances of the tear film.[5–10] A recent study using electrical impedance to measure tear osmolarity found that dry eye disease

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could be diagnosed with a sensitivity of 87% and a specificity of 81% when 316 mOsm/L was used as a cutoff.[9] In another study, tear osmolarity had superior diagnostic performance over other dry eye tests, including tear break up time, corneal staining, conjunctival staining, Schirmer's test, and meibomian gland grading. In that study, a tear osmolarity cutoff of 312 mOsm/L yielded a sensitivity of 73% and a specificity of 92% for diagnosing dry eye.[10]

Many systemic diseases such as diabetes can lead to DED through a variety of mechanisms.[11–14] Although the association between diabetes and dry eye is complex,[15] most studies support that diabetics experience high rates of DED.[15–20] In one study, 53% of subjects with either diabetes or borderline diabetes had self-reported, clinically significant dry eyes.[15] When severe, dry eye can cause ocular surface abnormalities such as superficial punctate erosions, epithelial defects, and corneal ulcers, which can lead to permanent corneal scarring. It is important to diagnose and treat dry eye in patients with diabetes, because they are already at risk for developing corneal problems. One study reported that 47%–64% of diabetic patients have primary corneal lesions during their lifetime.[21]

As tear osmolarity has been proposed as an objective test to diagnose and follow DED,[1] we sought to examine whether this would be a useful test in diabetic subjects, with the hope that an early diagnosis of DED could help prevent complications and improve quality of life. Despite numerous studies describing an association between diabetes and DED, to our knowledge, there are few publications describing tear osmolarity as a marker of dry eye severity in diabetes.[22–24] Additionally, we sought to examine how self-reported dry eye severity related to tear osmolarity in this population. We hypothesized that diabetic subjects would have increased dry eye symptoms and signs, including increased tear osmolarity, and that these would correlate with various parameters of diabetic control and complications. To test this hypothesis, we analyzed the relationship between tear osmolarity and dry eye symptoms in patients with type 1, type 2, and steroid-induced diabetes.

Materials and methods

Subjects were recruited from ophthalmology and endocrinology practices at an academic medical center during the summers of 2010 and 2012. Inclusion criteria were age over 18 years and a diagnosis of diabetes. Exclusion criteria were similar to previous studies of dry eye and tear osmolarity and included history of any significant ocular surface disease or ocular inflammation (other than keratoconjunctivitis sicca), history of ocular surgery within the past year, contact lens wear during the previous month, and the use of eye medications or artificial tears within 2 hours of checking tear osmolarity.[25,26] Past medical history, including medications, medical conditions, ocular history, years of diabetes, use of insulin, and a hemoglobin A1c (HbA1c) value within the last 3 months was obtained. Symptoms of DED were assessed with the ocular surface disease index (OSDI; Allergan, Inc, Irvine, CA, USA). The OSDI consists of 12 questions on symptoms within the past week and yields scores ranging from 0 (least severe) to 100 (most severe). A score of 12 is typically used as a cutoff for normal, 13–22 for mild dry eye, 23–32 for moderate dry eye, and ≥33 for severe dry eye.[27,28]

Tear osmolarity was measured in each eye with the TearLab® Osmolarity System (TearLab Corporation, San Diego, CA, USA). The system was stored in a temperature and humidity controlled environment, and these values were logged prior to each measurement of tear osmolarity. The system was calibrated at the beginning of each study day according to the manufacturer's instructions; the test cards used for each tear osmolarity measurement were from the same lot numbers as the test cards used to calibrate the machine each day. Tear samples were collected atraumatically from the lateral tear meniscus of the right eye and then the left eye using Pen 1 only for all measurements. A tear osmolarity value of 305 mOsm/L was used as the cutoff for mild dry eye,[6] and 316 mOsm/L was used as the cut-off for more severe dry eye disease.[29]

Statistical analysis

As recommended by the TearLab® manufacturer, statistical analysis was performed using the maximum osmolarity measurement value of the two eyes. Unless specifically stated, the osmolarity in this analysis will refer to the maximum osmolarity measurement of the two eyes. Statistical analysis using the average tear osmolarity of both eyes is presented in the supplementary materials (Table S1, Table S2 and Figure S1). Patient characteristics with continuous measurements were assessed using Spearman rank-order correlation coefficients to examine pairwise relationships with tear osmolarity or OSDI scores. The differences in tear osmolarity or OSDI between different levels of categorical characteristics were compared using one-way analysis of variance (ANOVA). All analysis was performed in Statistical Applications Software version 9.3 (SAS Inc, Cary, NC, USA).

Results

Subject characteristics

Fifty subjects (38 females and 12 males) with a mean (±standard deviation [SD]) age of 54.6±13.4 years, ranging

from 19 to 73 years old were recruited (Table 1). The majority of subjects were female (76%), African American (56%), and/or had type 2 diabetes (82%). Sixty percent of subjects required insulin treatment, 24% of subjects had a diagnosis of diabetic nephropathy, 18% of subjects had a diagnosis of diabetic retinopathy, and 38% of subjects had a diagnosis of peripheral neuropathy. Thirty-six percent of subjects had an HbA1c value below 7.0% within the previous 3 months, and 20% of subjects had an HbA1c ≥9.0%. Fifteen (30%) subjects reported current use of artificial tears, with frequency ranging from once per week to three times per day. None of the patients reported recent use of topical cyclosporine or ophthalmic ointments. Twenty-seven subjects (54%) had a tear osmolarity ≤305 mOsm/L, and ten subjects (20%) had a tear osmolarity ≥316 mOsm/L (Table 1). The mean of the patients' maximum tear osmolarity was 304.6±12.7 mOsm/L (Table 1).

Based on OSDI symptom scores, 24 subjects were classified as normal (48%), eight subjects had mild dry eye (16%), nine subjects had moderate dry eye (18%) and nine subjects had severe dry eye (18%; Table 1).

Table 1 Baseline characteristics of subjects

Characteristic	N (%)
Demographic	
Age	
Mean ± SD	54.6±13.4
Sex	
Female	38 (76%)
Male	12 (24%)
Race	
White	17 (34%)
African American	28 (56%)
Other	5 (10%)
Dry eye	
OSDI	
Normal (0–12)	24 (48%)
Mild (13–22)	8 (16%)
Moderate (23–32)	9 (18%)
Severe (33–100)	9 (18%)
Mean ± SD	19.3±18.2
Maximum tear osmolarity (mOsm/L)	
Normal (≤305)	27 (54%)
Mild DED (>305–<316)	13 (26%)
Severe DED (≥316)	10 (20%)
Mean ± SD	304.6±12.7
Average tear osmolarity	
Normal (≤305)	35 (70%)
Mild DED (>305–<316)	14 (28%)
Severe DED (≥316)	1 (2%)
Mean ± SD	300.2±10.1
Artificial tears	
No	35 (70%)
Yes	15 (30%)
Diabetes severity	
Diabetes type	
Type 1	4 (8%)
Type 2	41 (82%)
Steroid-induced	5 (10%)
Years of diabetes	
<5 years	16 (32%)
5 to 10 years	12 (24%)
>10 to 20 years	14 (28%)
>20 years	8 (16%)
Mean ± SD	11.4±9.0
Insulin	
No	20 (40%)
Yes	30 (60%)
Years of insulin	
Never	20 (40%)
≤5 years	20 (40%)
>5 years	10 (20%)
Mean ± SD	4.5±7.1
Hemoglobin A1c	
<7%	18 (36%)
7%–<9%	17 (34%)
≥9%	10 (20%)
Unknown	5 (10%)

(*Continued*)

Associations with tear osmolarity and dry eye symptoms (OSDI)

On average, men had higher osmolarity than women (mean, 311.8 mOsm/L [95% confidence interval {CI} 305.1, 318.5] versus [vs] 302.3 mOsm/L [298.5, 306.1], P=0.02) (Table 2). Among our study population, age, race, use of artificial tears, duration of diabetes, years of insulin use, and HbA1c were not significantly associated with tear osmolarity (Tables 2 and 3).

There was no significant effect of age, race, sex, years of insulin use, or HbA1c value on OSDI symptom scores in our study population (Tables 2 and 3). Longer duration of diabetes was associated with lower OSDI scores (r=–0.35, P=0.01) (Table 3).

Subjects with higher tear osmolarity had significantly lower OSDI values (r=–0.29, P=0.04) (Figure 1 and Table 3) with 13 of 24 (54%) nonsymptomatic (OSDI <13) patients having high osmolarity (>305), compared with ten of 26 (38%) symptomatic patients (OSDI ≥13). Subjects using artificial tears had worse OSDI scores than those not using artificial tears; however, this finding was not statistically significant (25.6 [16.7, 34.4] vs 16.7 [10.9, 22.5], P=0.11) (Table 2).

Discussion

Tear osmolarity and diabetes

Our population of diabetic subjects had an average maximum tear osmolarity of 304.6±12.7 mOsm/L with 46% having a tear

Table 1 (*Continued*)

Characteristic	N (%)
Mean ± SD	7.9±1.9
Peripheral neuropathy	
No	27 (54%)
Yes	19 (38%)
Unknown	4 (8%)

Abbreviations: N, number; SD, standard deviation; DED, dry eye disease; OSDI, ocular surface disease index.

osmolarity >305 mOsm/L, which is consistent with mild dry eye using the cutoffs described by Versura et al.[6] Our findings are similar to the findings of Najafi et al,[24] who found that in 243 subjects with type 2 diabetes, the mean tear osmolarity using the TearLab® system was 302±14 mOsm/L. The slightly lower average tear osmolarity found in their study is not unexpected, as they reported the mean of the average tear osmolarity of both eyes instead of the average maximum tear osmolarity.

However, tear osmolarity in our diabetic population was lower than that found by Sağdik et al,[22] who found an average tear osmolarity of 320±22 mOsm/L in diabetic subjects and 308±18 mOsm/L in controls. Glycemic control was similar in our study and that of Sağdik et al, with a mean HbA1c of 7.9% in both studies. One possible explanation for the difference in tear osmolarity is that Sağdik et al required an eye drop washout period of 12 hours and ointment washout of 5 days, whereas our study required that subjects not use any eye drops for a period of 2 hours as recommended by TearLab and as employed by other tear osmolarity studies.[25,26,30] Because 30% of our subjects reported using artificial tears, future studies in our population with a longer washout period may find a maximum tear osmolarity closer to the value found by Sağdik et al.[22]

We also studied whether or not markers of diabetic severity correlated with tear osmolarity. We did not find a significant relationship between tear osmolarity and the duration of diabetes, HbA1c level, or use of insulin. This is similar to the findings of Aragona et al,[23] who found that tear osmolarity in patients with type 1 diabetes was not correlated with HbA1c, diabetes duration, or retinopathy. Similarly, Sağdik et al[22] did not find a correlation between tear osmolarity and HbA1c; however, their study did find that tear osmolarity increased with duration of diabetes.[22]

Relationship of dry eye symptoms with diabetic severity markers

Based on OSDI symptom scores, 52% of our diabetic population had at least mild dry eye, and subjects with a

Table 2 Differences in categorical variables by either tear osmolarity or OSDI using maximum tear osmolarity for analysis

Baseline characteristics	Maximum tear osmolarity (mOsm/L)		OSDI	
	Mean (95% CI*)	*P*-value**	Mean (95% CI*)	*P*-value**
Demographics				
Sex				
Female	302.3 (298.5, 306.1)	0.02	21.0 (15.4, 26.7)	0.24
Male	311.8 (305.1, 318.5)		14.1 (4.0, 24.1)	
Race				
White	303.4 (297.5, 309.3)	0.64	18.2 (9.8, 26.6)	0.49
African American	304.5 (299.9, 309.1)		21.4 (14.9, 28.0)	
Other	309.4 (298.5, 320.3)		11.5 (0, 27.0)	
Dry eye				
Artificial tears				
No	305.6 (301.4, 309.7)	0.40	16.7 (10.9, 22.5)	0.11
Yes	302.3 (296.0, 308.6)		25.6 (16.7, 34.4)	
Diabetes severity				
Diabetes type				
Type 1	305.5 (293.3, 317.7)	0.62	4.0 (0, 20.4)	0.03
Type 2	305.1 (301.3, 309.0)		19.0 (13.8, 24.1)	
Steroid-induced	299.4 (288.5, 310.3)		34.8 (20.1, 49.5)	
Insulin				
No	304.5 (299.0, 309.9)	0.94	16.7 (8.9, 24.5)	0.39
Yes	304.7 (300.2, 309.2)		21.1 (14.7, 27.5)	
Peripheral neuropathy				
No	301.9 (297.4, 306.4)	0.10	18.2 (11.5, 25.0)	0.68
Yes	306.2 (300.8, 311.5)		21.9 (13.9, 29.9)	
Unknown	315.3 (303.5, 327.0)		14.7 (0, 32.2)	

Notes: *95% confidence interval (CI). Negative values for OSDI have been changed to zero; **analysis of variance (ANOVA).
Abbreviation: OSDI, ocular surface disease index.

Table 3 Correlations between continuous variables and either tear osmolarity or OSDI using maximum tear osmolarity for analysis

Characteristic	Maximum tear osmolarity		OSDI	
	rho*	*P*-value	rho*	*P*-value
Age	–0.12 (–0.39, 0.16)	0.39	–0.04 (–0.31, 0.25)	0.81
OSDI	–0.29 (–0.53, –0.02)	0.04	n/a	
Maximum tear osmolarity	n/a		–0.29 (–0.53, –0.02)	0.04
Years of diabetes	0.06 (–0.22, 0.34)	0.67	–0.35 (–0.57, –0.08)	0.01
Years of insulin	0.07 (–0.21, 0.35)	0.61	–0.13 (–0.40, 0.15)	0.36
Hemoglobin A1c	–0.02 (–0.31, 0.28)	0.91	0.07 (–0.23, 0.36)	0.64

Note: *Spearman correlation coefficient with 95% confidence interval limits.
Abbreviations: OSDI, ocular surface disease index; n/a, not applicable.

shorter duration of diabetes reported the greatest symptoms, whereas patients with longstanding diabetes reported fewer symptoms. The frequency of dry eye symptoms in our study is similar to that of Manaviat et al,[31] who found that 54% of 199 diabetic subjects had dry eye symptoms. In contrast to our study, Manaviat et al found a significant positive association between dry eye syndrome and the duration of diabetes. However, our finding that patients with longstanding diabetes had fewer DED symptoms is in agreement with previous evidence showing that, over time, poorly controlled diabetes can result in reduced corneal sensation,[32–36] and therefore, reduced dry eye symptoms. Moreover, in vivo confocal microscopy has shown that diabetic patients have reduced corneal nerve fiber length, thickness, and branching compared with non-diabetic controls.[37–39] Similarly, patients with severe diabetic neurotrophic keratopathy exhibit signs of severe dryness with very few symptoms.[11]

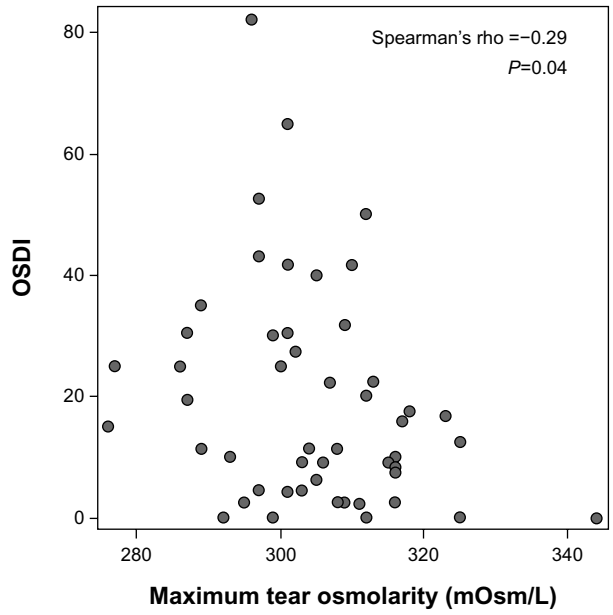

Figure 1 Maximum tear osmolarity versus OSDI.
Note: There was a statistically significant negative correlation between OSDI and tear osmolarity (r=–0.29, P=0.04) when the data were analyzed using the maximum tear osmolarity from the two eyes.
Abbreviation: OSDI, ocular surface disease index.

We did not find a relationship between DED symptoms and HbA1c in our study. This is in contrast to the results of previous research,[17,19,24,31] including the results of Kaiserman et al,[17] who found a greater use of artificial tears among diabetic subjects with a higher HbA1c. It is possible that HbA1c levels did not correlate with dry eye symptoms in our study because HbA1c reflects only the average blood glucose level over the previous 3 months. Therefore, HbA1c levels may not necessarily correlate with decreased corneal sensation, which can affect the perception of dry eye symptoms and likely takes years of poorly controlled diabetes to develop.

Tear osmolarity and dry eye symptoms in diabetic patients

In our diabetic population, subjects with higher tear osmolarity reported fewer dry eye symptoms. This association is the opposite of that found in a previous study showing a significant small positive correlation between tear osmolarity and OSDI score among the general population and an even stronger correlation among moderate dry eye subjects.[6] One possible explanation for the negative correlation seen in our study is that, as mentioned previously, diabetic subjects may have reduced corneal sensitivity,[34,35] which could lead to decreased awareness of dry eye symptoms. Reduced corneal sensation can also lead to a reduced blink rate and increased tear evaporation.[14] In addition, diabetic patients also show reduced tear production, with some studies showing a reduction in basal tear production[32,35] and others showing a reduction in reflex tearing only.[33] Both increased tear evaporation and reduced tear production can result in increased tear osmolarity.[40] Therefore, it is possible that diabetic patients with a higher tear osmolarity resulting from increased tear evaporation and reduced tear production may also report a lower OSDI score because of their decreased corneal sensation.

Limitations

Our study did not have sufficient power to determine whether there is a relationship between type of diabetes (type 1, type 2,

steroid-induced), diabetic microvascular complications (retinopathy, neuropathy, or nephropathy) and tear osmolarity or DED symptoms. Future studies enrolling a larger number of diabetic subjects that also include analysis of corneal sensitivity and other markers of DED will be helpful in diagnosis and treatment of dry eye disease in this population.

Conclusion

Approximately half of our diabetic subjects had a tear osmolarity consistent with dry eye disease and 52% reported DED symptoms consistent with at least mild dry eye disease, but we found that subjects with higher tear osmolarity reported fewer dry eye symptoms. We also found that subjects with a longer duration of diabetes reported fewer dry eye symptoms. Therefore, health care providers should be aware that patients with long-standing diabetes may not experience symptoms and seek care. It is important that diabetics receive regular eye exams not only to check for signs of diabetic retinopathy, but also to evaluate patients for occult dry eye disease which could be affecting their vision.

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Supplementary materials

Table S1 Differences in categorical variables by either tear osmolarity or OSDI

Baseline characteristics	Average tear osmolarity (mOsm/L)		OSDI	
	Mean (95% CI*)	*P*-value**	Mean (95% CI*)	*P*-value**
Demographics				
Sex				
Female	298.3 (295.3, 301.3)	0.01	21.0 (15.4, 26.7)	0.24
Male	306.2 (300.8, 311.5)		14.1 (4.0, 24.1)	
Race				
White	298.6 (293.8, 303.3)	0.59	18.2 (9.8, 26.6)	0.49
African American	300.5 (296.8, 304.2)		21.4 (14.9, 28.0)	
Other	303.6 (294.9, 312.3)		11.5 (0, 27.0)	
Dry eye				
Artificial tears				
No	300.8 (297.5, 304.1)	0.51	16.7 (10.9, 22.5)	0.11
Yes	298.7 (293.7, 303.8)		25.6 (16.7, 34.4)	
Diabetes severity				
Diabetes type				
Type 1	300.6 (290.9, 310.3)	0.49	4.0 (0, 20.4)	0.03
Type 2	300.7 (297.7, 303.8)		19.0 (13.8, 24.1)	
Steroid-induced	295.1 (286.4, 303.8)		34.8 (20.1, 49.5)	
Insulin				
No	299.8 (295.4, 304.2)	0.82	16.7 (8.9, 24.5)	0.39
Yes	300.4 (296.8, 304.0)		21.1 (14.7, 27.5)	
Peripheral neuropathy				
No	297.5 (293.9, 301.1)	0.06	18.2 (11.5, 25.0)	0.68
Yes	302.3 (298.0, 306.5)		21.9 (13.9, 29.9)	
Unknown	308.3 (299.0, 317.5)		14.7 (0, 32.2)	

Notes: *95% confidence interval. Negative values for OSDI have been changed to zero; **analysis of variance (ANOVA).
Abbreviations: CI, confidence interval; OSDI, ocular surface disease index.

Table S2 Correlations between continuous variables and either tear osmolarity or OSDI

Characteristic	Average tear osmolarity (mOsm/L)		OSDI	
	rho*	*P*-value	rho*	*P*-value
Age	–0.13 (–0.39, 0.16)	0.38	–0.04 (–0.31, 0.25)	0.81
OSDI	–0.18 (–0.44, 0.10)	0.20	n/a	
Average tear osmolarity	n/a		–0.18 (–0.44, 0.10)	0.20
Years of diabetes	0.07 (–0.21, 0.35)	0.61	–0.35 (–0.57, –0.08)	0.01
Years of insulin	0.06 (–0.22, 0.34)	0.66	–0.13 (–0.40, 0.15)	0.36
Hemoglobin A1c	0.00 (–0.29, 0.30)	0.98	0.07 (–0.23, 0.36)	0.64

Note: *Spearman correlation coefficient with 95% confidence interval limits.
Abbreviations: OSDI, ocular surface disease index; n/a, not applicable.

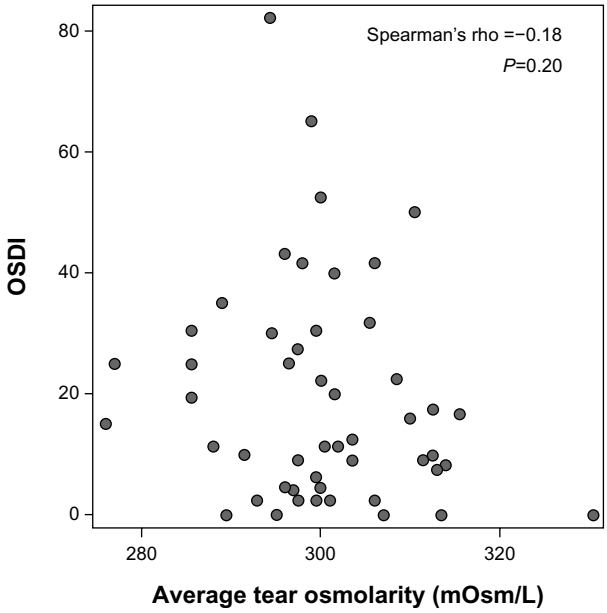

Figure S1 Average tear osmolarity versus OSDI.
Note: Subjects with a higher average tear osmolarity trended toward having a lower OSDI value.
Abbreviation: OSDI, ocular surface disease index.