Differences in Clinical Parameters and Tear Film of Tolerant and Intolerant Contact Lens Wearers

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Purpose. To determine whether intolerance to contact lens wear is attributable to clinical or protein characteristics of the tear film.

Methods. Thirty-eight subjects participated; 20 were successful contact lens wearers and 18 had discontinued contact lens wear because of discomfort. Baseline tear film (no lens wear) was analyzed with a range of clinical measurements and protein analyses (lactoferrin, sIgA, and lysozyme). Comfort was determined after 6 hours of lens wear, and differences in tear film characteristics between subject groups were determined. In half of the subject group ($n = 19$), discriminant analysis was used to develop an equation for predicting the likelihood of intolerance to lens wear. Sensitivity and specificity were determined by testing the formula on the remaining subjects. These formulas were also tested on a separate group of subjects enrolled in a contact lens–wearing trial.

Results. Tear volume (meniscus height and phenol red thread test) and tear stability (noninvasive tear break up time [NI-TBUT]) were significantly reduced in intolerant wearers ($P < 0.05$). A greater number of symptoms were reported by intolerant than by tolerant wearers ($P < 0.05$). Tolerance was associated with clinical but not protein characteristics of the tear film. Formulas best able to predict contact lens intolerance included NI-TBUT, number of symptoms experienced, and tear film meniscus height. Formulas had high sensitivity, and specificity which ranged from 29% to 57%.

Conclusions. Contact lens intolerance appears to be best predicted by a combination of clinical variables, including tear film stability, tear volume, and symptom reporting. (*Invest Ophthalmol Vis Sci.* 2003;44:5116–5124) DOI:10.1167/iovs.03-0685

Signs of tear film disturbance during contact lens wear may appear to be similar to those observed in dry eye.[1] Contact lens–induced dry eye falls into both the evaporative and tear-deficient classes of dry eye, as classified by the National Eye Institute.[2,3] The sensation of dryness can cause many patients to reduce their contact lens wearing time or may render them intolerant of lens wear.[4] Successful wearers may still complain of dryness, but are able to persist in lens wear for more than 9 hours per day.[5] After 2 years of daily disposable contact lens wear, 85% of patients were satisfied with their comfort and vision, whereas 15% were dissatisfied with lens wear because they experienced discomfort and dryness.[6] In a study examining the reasons for discontinuation of wear, 51% of subjects cited discomfort as the principal reason.[7]

The tear film is an interactive system that includes mucins, proteins, lipids, lipoproteins, and glycolipids. These components form a layered or phaselike film, with estimates of the thickness ranging from 35 μm.[8] to 3 μm.[9,10] The volume of the tear film has been determined with fluorescence techniques to be approximately 6 to 7 μL.[11] The production rate has been measured by various researchers and found to be in the range of less than 1 to 1.2 μL/min for nonstimulated (basal) tears and greater than 5 μL/min for stimulated (reflex) tears.[11,12] The tear film alterations responsible for the development of dry eye are probably complex and involve not only tear quantity but also tear quality.[13] Precorneal noninvasive tear break-up time (NI-TBUT) has been used to assess the stability of the tear film and can range in time from very poor (<10 seconds) to very good (>30 seconds).[14] Commonly, dry eye and symptomatic patients have a precorneal NI-TBUT in the region of 3 to 10 seconds.[15,16] The NI-TBUT during soft contact lens wear falls within this range (6–8 seconds).[17–19] The repeatability of the NI-TBUT technique has been questioned, and high variability may exist within and between subjects[20–22] and between instruments,[23,24] although several groups still use this method of measurement.[25–27] Another measurement of tear stability, which includes the subjects' personal feelings of ocular dryness, is the measurement of blink interval,[28] and the time between blinks is quicker in those with keratoconjunctivitis sicca than in healthy control subjects with a stable tear film.[29]

Other common variables reported to be related to ocular dryness and dry eye complications include the volume of aqueous tears available to cover the ocular surface and the concentration of lactoferrin in tears. Decreases in lactoferrin concentration are associated with decreases in tear production from the lacrimal gland.[30] Lactoferrin concentration has been shown to be both a good and bad predictor of tear film stability or volume.[30,31] In Sjögren's syndrome, Vitali et al.[22] found variable lactoferrin results, which were not concordant with other more common diagnostic tests such as rose bengal staining, Schirmer test, and ocular symptoms. Tear meniscus height and radius are significantly diminished in dry eye.[32] The phenol red thread test (PRTT) also purports to measure tear volume in the lower conjunctival sac.[33,34] Normal values are considered to be approximately 10 to 20 mm.[34] In the current investigation, we sought to relate protein characteristics of the tear film and clinical variables, to help in our understanding of tear film dynamics in contact lens–induced intolerance.

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TABLE 1. Group 1 and 2 Demographics

Contact Lens Preference	Group 1 (*n*)	Group 2 (*n*)	Age (y)	Gender (M/F*)
Tolerant	10	10	21–38	7/13
Intolerant	9	9	25–39	2/16

* The number of females using oral contraceptives at the time of each study was in group 1, three tolerant and two intolerant contact lens wearers, and in group 2, four tolerant and two intolerant contact lens wearers. Hormonal regulation of the tear film has been shown to affect mucin and other proteins, although recent estradiol studies indicate that contraceptives have no effect on the tear film.[3,58]

METHODS

Subject Selection

Subjects with a history of contact lens wear participated in this study (Table 1). Nineteen tolerant and previously intolerant lens-wearing subjects were recruited for tests over 3 days (group 1). A second group (group 2) was enrolled a month later to retest the findings in the first group (group 2, $n = 19$). All subjects signed informed consent, the protocol was approved by the Institutional Ethics Committee of the University of New South Wales, and the guidelines of the Declaration of Helsinki were adhered to.

Procedures

To determine the subject's tolerance level, subjects wore Vifilcon A lenses (FDA group IV; CIBAVision Corp., Duluth, GA). After 6 hours, the subjects were asked to describe any symptoms they had felt and to rate their tolerance to daily soft contact lens wear. Subjects did this by selecting whether they could be tolerant of lens wear in one of the following periods: for 6 hours or less, for a full working day (9 hours), or for 2 days of consecutive daily wear and daily wear of longer than 2 days (Fig. 1). Tolerance to lens wear was subsequently defined as the ability to wear lenses regularly during one working day (9 hours) or longer. After contact lens wear, subjects did not wear lenses for at least 1 day and then completed the clinical and biochemical assessments described later in the absence of contact lens wear. All the clinical and biochemical tests were repeated on 2 or 3 days to determine repeatability (paired *t*-test, repeated measures ANOVA, and the intraclass correlation [ICC]) of the measurements.

On arrival, the subjects completed a modified McMonnies dry eye history questionnaire to ascertain the number, type, and frequency of dryness symptoms.[35] This questionnaire elucidated any recent medical and medication history that might have affected lacrimal tear production (Schein OD, et al. *IOVS* 1997;38:ARVO Abstract 1023). Symptoms included in the questionnaire were ocular soreness, scratchiness, dryness, and grittiness (from the original McMonnies questionnaire) and burning, stinging, foreign body sensation, and itchiness (which were added to form the modified McMonnies questionnaire). The temperature and humidity of the clinical room were 23°C to 24°C and 41% to 44%, respectively, and these levels were maintained over the month of testing.

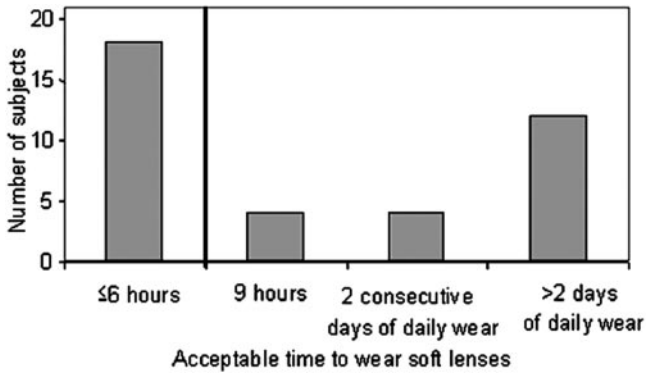

FIGURE 1. Levels of tolerance selected by subjects wearing soft group IV contact lenses.

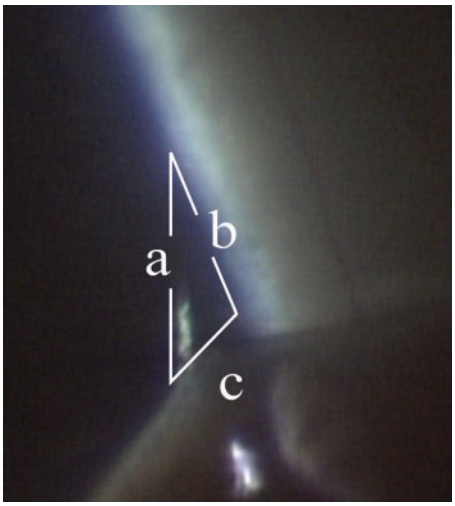

FIGURE 2. Measurement of the lower lid tear film meniscus including height and area by video biomicroscopy. Cross-sectional area of meniscus = $\{\sqrt{[s(s-a)(s-b)(s-c)]}\}$/(magnification factor)^2, where $s = (a + b + c)/2$. Tear film height = measured height a (mm)/magnification factor (1 mm = 60 mm).

Maximum Blink Interval

The maximum blink interval (MBI) is the length of time a subject could hold his or her gaze (stare) on an object at a distance of approximately 3 m before ocular irritation occurred and without reflex tearing.[29] This usually meant passing the first urge to blink, which occurred in 3 to 5 seconds and concentrating on the next ocular feeling of dryness or irritation and then blinking. A stopwatch was used to record the MBI, and three consecutive readings for each eye were averaged (the intrasubject variability was approximately 17% of the mean).

Phenol Red Tear Test

Patients were asked to keep their eyes open (blinking gently if necessary) for 15 seconds while a phenol-red–impregnated cotton thread (Zone-Quick; Menicon Co., Ltd., Nagoya, Japan) was placed in their lower conjunctival sac. This test is based on the Hamano cotton thread test measuring tear volume in the lower meniscus sac.[33] Three consecutive readings for each eye were averaged and results reported as millimeters of tear wetting (the intrasubject variability was approximately 22% of the mean).

Meniscus Images

The inferior tear meniscus height (tear prism) was recorded by three-color charge coupled device video camera (Sony, Tokyo, Japan) attached to a slit-lamp biomicroscope (30 SL/M; Carl Zeiss Meditec, Oberkochen, Germany). The tear prism near the middle of the lid margin was observed by using an optic section with the microscope at 45° to the light path, to form a specular reflection of the prism. The magnification was fixed for each measurement where 1 mm = 60 mm. The images, one for each eye, were measured manually for height and prism area (triangular shape) and averaged. Measurements were adjusted for magnification (Fig. 2).

Tear Collection

Basal (open-eye) tears were collected with glass microcapillary tubes.[12,36,37] The time taken for tears to reach a specified point was

recorded as flow rate (microliters per minute). Tear collection continued until a minimum of 15 μL was collected on 1 day from a combination of both eyes. In some cases, this took up to 40 minutes without reflex stimulation and no irritation (and often subjects rested for 5 minutes between each 5 μL collected). After collection, tears were centrifuged at 1000*g* for 5 minutes to remove debris, divided into smaller aliquots, and stored at −80°C until all subjects had completed clinical examination.

Noninvasive Tear Break-up Time

NI-TBUT was determined noninvasively using a custom-made tearscope on a modified slit lamp. The technique was based on that of Guillon and Guillon[38] as described in Carney et al.[39] NI-TBUT was the time measured, in seconds, between the full opening of the eyelids after a complete blink and the first break in the tear film. Three consecutive readings for each eye were averaged (the intrasubject variability was approximately 8% of the mean). The tear break-up appeared as spot (type 1) or streak (type 2) patterns (Bitton E, et al. *IOVS* 1994;35:ARVO Abstract 1576).

Conjunctival Redness

The Cornea and Contact Lens Research Unit (CCLRU) decimalized grading scale[40] (range, 1–4) was used to assess the redness of both eyes in the nasal, temporal, superior, and inferior quadrants for both the limbal and bulbar regions.[40] Intrasubject variability did not exceed 16% of the mean.

Lipid Layer Appearance

Slit lamp examination of a subject's ocular lipid layer in both eyes was measured on a graded scale (0–5),[38] where 0 is no lipid, 1 is an open meshwork, 2 is a tight meshwork, 3 is a flow pattern, and 4 is an amorphous pattern, and 5 is a pattern with colored fringes.

Osmolality

Tear osmolality (milliosmoles per kilogram) was measured with a vapor pressure osmometer (Wescor; Amscorp, Sydney, Australia) which required 7 μL of tears. Tears were collected as described previously and were thawed to room temperature after calibration of the osmometer. As the measured decrease in vapor pressure is due to electrolytes, it is likely that this method reflects tonicity rather than osmotic pressure.[41] Intrasubject variability did not exceed 9% of the mean.

Total Protein Content

Total protein was determined by semiquantitative assay (bicinchoninic acid; Bio-Rad, Richmond, CA). Standards of bovine serum albumin ranged from 0 to 1 mg/mL in 0.1 M Tris base (pH 11.0) buffer. Tear samples (10 μL) were diluted 1:50 or 1:100 in Tris (pH 11.0) buffer. The data were expressed as the mean of two samples from each eye and data from both eyes were combined.

Lactoferrin and sIgA

A commercially available enzyme-linked immunosorbent assay (ELISA; Oxis International, Inc., Portland, OR) was used for lactoferrin according to the manufacturer's instructions and a published sandwich ELISA method was used for sIgA.[42] Samples were tears diluted to 1:10,000 and 1:20,000 in sample diluting phosphate buffer supplied for lactoferrin and tears diluted 1:1000 in PBS containing 0.1% (vol/vol) Tween 20 for sIgA. The data were expressed as the mean of two samples from each eye and both eyes combined.

Lysozyme

A turbidimetric assay[43] was used and included 20 μL human milk lysozyme standards (0.016–1.0 mg/mL; Sigma-Aldrich, St. Louis MO) and 20 μL tear samples (diluted 1 in 2 or 1 in 4 in PBS; pH 7.4). Samples and standards were mixed with 20 μL *Micrococcus lysodeikticus* (1 mg/mL in PBS; Sigma-Aldrich). Changes in optical density after 15 minutes at 35°C were measured at 450 nm and converted to micrograms per microliter of active lysozyme concentration using a standard curve. The data were expressed as the mean of two samples from each eye and both eyes combined.

Statistical Analysis

The results of a pilot study[44] were used to determine the sample size needed based on NI-TBUT, PRTT, MBI, and meniscus height on computer (GPower program ver. 2.0).[45] This indicated that two subject groups (tolerant versus intolerant) of at least nine people (power 80%; confidence 95%) were needed. The following analyses were performed with statistical-analysis software (The Statistical Package for Social Sciences; SPSS for Windows, version 10.0.05; SPSS Sciences, Chicago, IL).

All variables were tested for outliers by using box plots. After computer-generated identification of outlying data points for each variable, internal logic was applied before accepting the removal of the data point. Removal of data points did not include removing the whole subject, but simply that point from a particular variable that was found to be outlying. This allowed outlying individual observations (possibly contaminated samples) to be left out of the final group for each test. This accounts for the variation in the number of observations included for different variables. Repeated measurements of variables for each subject were averaged. Data from both eyes were also averaged when available (these had been found to be consistent between eyes; data not presented). Variables were broadly classified as parametric or nonparametric after testing for a normal distribution. The criteria for classification of the variables included the measurement scale of the variable (i.e., dichotomous or decimalized grades) and sample size. Parametric variables: conjunctival redness, meniscus height and area, NI-TBUT, PRTT, MBI, tear flow rate, total protein concentration, lactoferrin, sIgA, lysozyme, and osmolality. Nonparametric variables: McMonnies total score, lipid layer appearance, number of symptoms, dry type, and tolerance level.

Analysis of Variation within Tear Film Variables. The diurnal and daily differences of the tear film clinical and protein variables were initially tested using a two-way, repeated-measures ANOVA to identify interaction effects. In most cases the interaction effects were significant and the data were then split by each factor and the paired *t*-test used to test the difference between the means. Where the effects of interaction were not significant, a multiple range test with Bonferroni correction was used to determine significant differences between groups. Nonparametric data were examined with the Friedman χ^2 test. The daily repeatability of variables was measured using the ICC. This correlation value is considered to indicate excellent reliability at approximately 0.7 and adequate at 0.4 or more.[46–48] ICCs provide insight into the correlation of two groups of repeated data and, together with ANOVA, results demonstrate the groups that are not significantly different and the subjects who show correlation between the two groups.[47] Variables were considered statistically different if $P < 0.05$ and the variance ratio (F) was greater than 3.8.

Analysis of Significant Differences within Tear Film Variables. All differences between the tolerant and intolerant subject groups were compared using the independent group *t*-test for parametric data (mean ± SD) and the Mann-Whitney test for the nonparametric data (median ± semiquartile range). Variables were considered statistically different if $P < 0.05$. The observed power of the tests between subjects was calculated using the univariate ANOVA.

Analysis of Association of Tear Film Variables. The biochemical and clinical data were examined for possible associations. Association of parametric data was measured using the Pearson correlation, and the Spearman ρ was used for nonparametric data. Correlation between variables was categorized as moderate (0.4–0.6), substantial (0.61–0.8), and almost perfect (0.8–1.0).[49]

Discriminant Analysis. Discriminant analysis was used to determine a formula to predict tolerance. In this analysis any missing values were replaced by means of the whole group. To determine a

TABLE 2. Tear Film Differences Observed Between Tolerant and Intolerant Contact Lens Wearers

	Tolerant Lens Wear Subjects			Intolerant Lens Wear Subjects			
Variables*	*n*†	Mean/Median	SD/Interquartile Range	*n*†	Mean/Median	SD/Interquartile Range	*P*‡
McMonnies total score	20	6.0	3–7	16	10.0	7–14	**0.012**
Number of symptoms (0–8)	20	1.5	1.0–2.0	18	3.0	2.5–4.5	**0.011**
Maximum blink interval (s)	20	28.9	14.0	16	14.6	5.7	**0.012**
Phenol red thread test (mm)	20	16.4	3.2	16	11.9	4.2	**0.017**
Meniscus height (mm)	20	0.43	0.11	17	0.31	0.09	**0.024**
Meniscus area (mm^2)	19	0.07	0.01	17	0.04	0.01	**0.001**
Noninvasive tear Break-Up Time (s)	20	20.2	5.6	18	13.2	3.2	**0.005**
Dry type (spot, 1) (streak, 2)	16	1	1–2	16	2	2	**0.001**
Limbal redness (1–4)	20	1.5	0.2	18	1.6	0.2	0.132
Bulbar redness (1–4)	20	1.8	0.3	17	1.8	0.2	0.817
Lipid layer appearance (0–5)	20	3	1–4	16	3	2–4	0.169
Tear flow rate (μL/min)	19	1.04	0.18	17	0.83	0.26	0.058
Total protein ($\mu g/\mu L$)	20	3.54	1.31	17	3.86	0.64	0.509
Secretory IgA ($\mu g/\mu L$)	20	0.87	0.11	17	0.72	0.22	0.084
Lactoferrin ($\mu g/\mu L$)	20	2.69	1.07	14	3.18	0.76	0.270
Lysozyme ($\mu g/\mu L$)	18	1.60	0.18	14	1.52	0.32	0.410
Osmolality (mOsmol/kg)	19	317.4	8.9	14	324.4	6.5	0.069

Data are the mean or median values for group 1 and group 2 combined; these were not statistically different from one another.

* Lipid layer appearance was graded 0–5. The McMonnies dry eye history questionnaire was used for both a total score and to measure the number of symptoms. The tear film meniscus height and area (at the lower lid) were calculated with slit lamp video images.

† The number of subjects varied according to any outlier requirements mentioned in the Methods section. The total number of subjects in both studies was 20 in the tolerant group (combined) and 18 in the intolerant group (combined).

‡ Bold type indicates significant at the 5% level.

formula, the software (SPSS) ran repeated mathematical equations within the program, using all but one subject, and then placed this one sample back into the equation to determine the "internal confidence" level. The formula was then tested to determine its robustness; assessing whether tolerance or intolerance was correctly identified for each subject. The computer program (SPSS) performed this for each of the 19 subjects until one selected formula gave the highest confidence level for every subject. All clinical and biochemical variables were added to the equation determination initially, then systematic removal of variables resulted in formulas with highest confidence level.

The formulas derived from the first 19 subjects (group 1) were tested on the second subject group ($n = 19$) to estimate sensitivity (those intolerant subjects correctly identified by the formula) and specificity (those tolerant subjects correctly identified) of the created formulas.[50] Similarly, discriminant analysis was used to derive formulas from data from the second group (group 2) and these were tested on the first data set (group 1).

Testing the Accuracy of the Predictive Formulas

These subjects were distinct from those enrolled in either group 1 or group 2. Twenty-seven previous contact lens wearers successfully completed this study. All subjects were fitted with Ocufilcon D lenses (Biomedics; Ocular Sciences Inc., San Francisco, CA; FDA group IV) and wore lenses for 6 hours during the day. At the end of the lens-wear period, the subjects were asked to rate their comfort in lenses and ocular dryness during lens wear on scales ranging from 0% to 100%. Comfort and dryness scores ranged between 5% and 100%, with 60% representing the median. Subjects were also asked to rate whether they were tolerant (could have worn lenses for longer than 6 hours) or intolerant (would not wear lenses for up to 6 hours).

The calculations for each formulas including the raw variable data, the mathematical calculation, and the negative or positive results for each subject were then converted into tolerance codes (1, tolerant; 2, intolerant). The tolerance code was aligned with the subjects' tolerance, comfort, and dryness in lenses. The preferences were masked until the clinical observations had been substituted into the selected formulas and the tolerance level calculated. This allowed the predictive power of each formula to determine first a tolerance level for each subject based on the given variables and then to be compared against the subjects' 6-hour tolerance level, comfort level, and dryness level. Correlations between tolerance measures and predictive formulas were measured using the Spearman ρ.

RESULTS

One tolerant and one intolerant subject reported very mild cases of meibomitis, but as the condition was not considered to be present at clinically significant levels, both subjects were included in the study. Differences between eyes in all subjects were not significant for all variables (for all tests $P > 0.6$, paired ANOVA); therefore, the data for both eyes were averaged before further analysis. No significant daily or diurnal variation was measured (data not shown; all $P > 0.14$ and ICC $\alpha > 0.54$, except for limbal and bulbar conjunctival redness scores: $P > 0.06$ and ICC $\alpha > 0.75$).

There were significant differences between the tolerant and intolerant contact lens wearers but not between groups, except for the tolerant group, where limbal conjunctival redness was higher on average in group 2 than in group 1 (2.0 vs. 1.5 with 0.2 SD; $P = 0.049$). However, the mean values recorded were within the expected between-observer variability[50] and therefore the differences were not considered to be clinically significant. In addition, the ICC α for the correlation of subject results was greater than 0.3. For the intolerant subjects, there were no significant differences.

Table 2 lists all the mean or median responses for each variable measured for both tolerant and intolerant contact lens wearers. The modified McMonnies total score and number of symptoms reported were significantly different between the tolerant and intolerant subjects. Tolerant subjects experienced on average only one symptom associated with dryness when not wearing lenses, whereas intolerant subjects experienced an average of three symptoms. The most common symptoms reported by all subjects were dryness, foreign body sensation, and stinging.

MBI and NI-TBUT were significantly lower in intolerant subjects than in tolerant subjects (an average of 29 to 15

TABLE 3. Significant Correlations between Baseline Variables of Tolerant and Intolerant Contact Lens Wearers

Variables*	Group 1§		Group 2§	
	P	*r*	*P*	*r*
Tolerance and number of symptoms experienced†	0.010 (n = 19)	+0.576	0.026 (n = 20)	+0.495
McMonnies total score and number of symptoms experienced†	0.025 (n = 17)	+0.540	0.0001 (n = 19)	+0.785
Tolerance and MBI (s)†	0.033 (n = 18)	−0.503	0.016 (n = 18)	−0.560
Tolerance and NI-TBUT (s)†	0.001 (n = 19)	−0.693	0.001 (n = 21)	−0.676
NI-TBUT and MBI (s)‡	0.019 (n = 18)	+0.547	0.022 (n = 18)	+0.534
Tolerance and Dry type†	0.005 (n = 18)	+0.632	0.0001 (n = 14)	+0.778
Tolerance and PRTT†	0.026 (n = 17)	−0.537	0.013 (n = 21)	−0.534
Tolerance and Meniscus area (mm^2)†	0.046 (n = 19)	−0.462	0.0001 (n = 17)	−0.842
Tolerance and Meniscus height†	0.013 (n = 19)	−0.558	0.027 (n = 19)	−0.507
Meniscus height and PRTT (mm)‡	0.051 (n = 17)	+0.506	0.022 (n = 19)	+0.506
Meniscus height (mm) and osmolality (mOsmol/kg)‡	0.014 (n = 18)	−0.566	0.047 (n = 13)	−0.438
Lactoferrin and Lysozyme protein concentration ($\mu g/\mu L$)‡	0.005 (n = 15)	+0.727	0.627 (n = 16)	+0.132

* Tolerance was the ability to wear contact lenses for longer than 6 hours, and intolerance was the inability to wear lenses for 6 hours; McMonnies Dry Eye history questionnaire total score (0–26); number of symptoms experienced with no lens wear (0–8); dry type pattern is coded 1 for spot and 2 for streak tear film break-up.

† Spearman ρ.

‡ Pearson correlation.

§ The number of subjects varies according to outlier requirements mentioned in the Methods section.

seconds and 20 to 13 seconds, respectively). The tear volume, as measured by tear meniscus area, was reduced significantly from 0.07 to 0.04 mm^2 in intolerant subjects. The PRTT result also was significantly lower in intolerant subjects (an average of 12 mm compared with 16 mm). Tear flow rate, sIgA concentration, and osmolality of the tears were significantly different at the 10% level. Total protein or lactoferrin concentration and lysozyme activity were not significantly different between tolerant and intolerant subjects. No differences were found in bulbar and limbal conjunctiva redness or the lipid layer appearance.

The data were analyzed for association between variables (r; Table 3). Results were considered significant if $r > 0.4$ and $P < 0.05$. The number of symptoms experienced by the subjects was associated with the level of tolerance selected by the subjects. Tolerance levels were inversely associated with both NI-TBUT and MBI, which supported the significant differences seen between the tolerant and intolerant groups. Tear film drying type significantly correlated with the tolerance level, where all intolerant subjects were found to have a streak pattern of tear film drying. The measures of aqueous volume (PRTT and meniscus area) correlated highly, whereas meniscus height correlated negatively with osmolality. Lysozyme and lactoferrin, both regulated lacrimal proteins, correlated highly in group 1 data but not in group 2 data. The protein variables did not correlate with any of the clinical measurements.

Discriminant Analysis for Determining a Formula to Predict Tolerance Levels in Soft Contact Lens Wear

Stepwise analysis was necessary to limit the number of variables that were selected to predict tolerance confidently. This analysis, in which all the variables were ranked according to statistical significance (Table 4; inclusion order), resulted in several predictive formulae with high confidence levels. Other analyses included only the clinical and biochemical variables to determine whether a formula from these variables could predict tolerance. Groups 1 and 2 were used to create initial formulas independently, which were then tested on the opposite group of subjects to determine specificity and sensitivity.

The formulas shown below were those selected as having both a high internal confidence level (>80%) and high external sensitivity (>80%). They were determined using either group 1 or group 2 data which changed the significance order of variables in each group and hence the order of inclusion in any formula (Table 4). Thus, the two different patient groups did not result in identical formulas. Biochemical variables were not predictive in any formula.

Formula 1. Obtained from group 2 data with all variables included using stepwise discriminant analysis: Outcome = dry type (4.452) + symptoms (0.411) − meniscus area (93.497) − 2.791 (mean: tolerant −2.984; intolerant 3.315; confidence 100%). A positive result suggests intolerance. When externally tested on group 1, this formula had 80% specificity and 89% sensitivity.

Formula 2. Obtained from group 2 data using all variables with dryness type removed, because it was a dichotomous variable, and using stepwise discriminant analysis: Outcome = NI-TBUT (0.131) − symptoms (0.512) + meniscus area (72.739) − 5.221 (mean: tolerant 1.816; intolerant −2.018; confidence 100%). A negative result suggests intolerance. When externally tested on group 1, this formula had 80% specificity and 89% sensitivity.

TABLE 4. The Variables Used to Determine Equations for Contact Lens Intolerance and their Inclusion Order in Stepwise Discriminant Analysis

All Variables*			
(Group 1)	(Group 2)	All Clinical†	All Biochemical†
NI-TBUT	Dry type	NI-TBUT	Lactoferrin
Osmolality	Meniscus area	Symptoms	Osmolality
Symptoms	Symptoms	Meniscus area	Total protein
Lactoferrin	NI-TBUT	Meniscus height	PRTT
Meniscus area	Total protein	McMonnies total	Flow rate
McMonnies total	Flow rate	PRTT	sIgA
PRTT	sIgA	MBI	Meniscus height
MBI	Lipid appearance	Lipid appearance	Meniscus area
Meniscus height	Meniscus height		Lysozyme
Dry type	Osmolality		
sIgA	McMonnies total		
Flow rate	MBI		
Total protein	PRTT		
Lysozyme	Lactoferrin		
Lipid appearance	Lysozyme		

* All variables for Groups 1 and 2 were included in the stepwise discriminant analysis according to their importance. They are shown in order of inclusion.

† Clinical or biochemical variables were used to predict tolerance, and these are listed in their inclusion order for stepwise discriminant analysis. (All clinical variables were chosen as those variables commonly used in optometry practice. All biochemical variables were chosen from measurements of protein, osmolality, and tear film volume.)

Formula 3. Obtained from group 1 data using only clinical variables with a stepwise discriminant analysis: Outcome = NI-TBUT (0.118) − symptoms (0.497) − 0.856 (mean: tolerant 1.059; intolerant −1.176; confidence 84.2%). A negative result suggests patient intolerance. When externally tested on Group 2 this formula had 100% specificity and 78% sensitivity.

Formula 4. Obtained using group 2 data and using only clinical variables with a stepwise discriminant analysis: Outcome = NI-TBUT (0.167) − symptoms (0.529) + meniscus height (6.176) − 4.434 (mean: tolerant 1.254; intolerant −1.393; confidence 89.5%). A negative result suggests intolerance. When externally tested on group 1, this formula had 80% specificity and 100% sensitivity.

Testing the Predicative Formulas on a Dispensing Contact Lens Clinical Trial Population

The tolerance during daily wear of lenses, subjective ratings of comfort in lenses, or ocular dryness sensation during lens wear of these subjects all correlated significantly ($P < 0.04$). The highest correlation coefficient was found between subjective comfort in lenses and dryness sensations (the more comfortable the lens, the less dry lenses felt; Table 5). Tolerance after 6 hours of lens wear showed good correlations with all formulas (Table 5).

Three of the formulas (Table 6) predicted with greater than 70% accuracy the tolerance of subjects according to their level of tolerance after 6 hours of lens wear. The other three equations used to determine subject tolerance all had accuracy of between 56% and 70%. Three formulas had the variables tear break-up time and number of ocular symptoms score in common. In general the formulas were better at predicting contact lens intolerance (sensitivity) than contact lens tolerance (specificity).

DISCUSSION

In this study, we examined two groups of in-house subjects for associations between tear film variables and tolerance to contact lens wear and then tested formulas derived from the subjects on a separate group of subjects who had been recruited to be enrolled in a contact lens wear trial. In our study, lens-intolerant subjects had a greater number of symptoms associated with ocular surface discomfort than lens-

TABLE 5. Correlations between Predicted Tolerance Outcomes and Subject Response Variables

		Predicted Outcome				Tolerance after 6 Hours' Lens Wear	Comfort in Lenses	Dryness in Lenses
Predicted Outcomes	Correlation Coefficient*	Formula 1	Formula 2	Formula 3	Formula 4			
Tolerance after 6 Hours' lens wear	Correlation coefficient	**0.402**	**0.524**	**0.570**	**0.625**	1.000		
	P†	***0.038***	***0.005***	***0.002***	***0.000***			
Comfort in lenses	Correlation coefficient	**0.433**	0.262	0.106	0.186	**0.484**	1.000	
	P†	***0.024***	*0.187*	*0.597*	*0.352*	***0.011***		
Dryness in lenses	Correlation coefficient	**0.466**	0.316	0.321	**0.399**	**0.564**	**0.779**	1.000
	P†	***0.014***	*0.108*	*0.102*	***0.039***	***0.002***	***0.000***	

$n = 27$. Bold type indicates significant correlation. Italic type indicates significant at the 5% level.

* Correlation coefficient − Spearman ρ.

† *P* is two-tailed.

TABLE 6. Specificity and Sensitivity of the Predictive Formulae on a Group of Subjects Entering a Contact Lens Wearing Clinical Trial

	Intolerance after 6 Hours' Lens Wear	Comfort in Lenses	Contact Lens Dryness
Formula 1			
1 → (Specificity)	4/14 (29)	4/13 (31)	4/15 (33)
2 → (Sensitivity)	13/13 (100)	14/14 (100)	15/15 (100)
Accuracy	12/27 (63)	18/27 (67)	19/27 (70)
Formula 2			
1 → (Specificity)	**8/14 (57)**	6/13 (46)	6/12 (50)
2 → (Sensitivity)	**12/13 (92)**	11/14 (79)	12/15 (80)
Accuracy	**20/27 (74)**	17/27 (63)	18/27 (67)
Formula 3			
1 → (specificity)	**7/14 (50)**	4/13 (31)	5/12 (41)
2 → (sensitivity)	**13/13 (100)**	11/14 (79)	13/15 (87)
Accuracy	**20/27 (74)**	15/27 (56)	18/27 (67)
Formula 4			
1 → (specificity)	**8/14 (57)**	5/13 (38)	6/12 (50)
2 → (sensitivity)	**13/13 (100)**	11/14 (79)	13/15 (87)
Accuracy	**21/27 (78)**	16/27 (59)	19/27 (70)

Sensitivity is the proportion of intolerant wearers (discomfort or dryness) who tested as intolerant in the screening test, and specificity is the proportion of tolerant wearers who tested as tolerant in the test. Data are subjects in the classification/total subjects in the group (percentage of total subjects in the group). See the Methods section for formulae. Bold type indicates most significant findings.

tolerant subjects. Intolerance to contact lens wear was associated with dryness symptoms both during contact lens wear and when lenses were not worn. The McMonnies dry eye survey is often used to elucidate the ocular symptoms of patients.[51] The McMonnies survey is said to have high specificity and sensitivity for dry eye diagnosis where a referent value of 14.5 or greater denotes dry eye.[51] However, in a report published previously using a smaller study group, the number of symptoms experienced by the subject, not the patient history, aided diagnosis of contact lens intolerance.[44] In the present study, the results of the modified McMonnies survey was significantly different between the two tolerance groups. However the actual scores were closely overlapping and ranged from 5 to 13 for intolerant and from 3 to 9 for tolerant subjects.

The highest correlation coefficients found with tolerance to lens wear over the two groups of subjects that were initially screened were NI-TBUT and dry type (both measures of tear film stability), followed by tear meniscus area (a measure of tear film volume). Fanti and Holly[52] have suggested that a person with marginal tear film deficiencies, while generally asymptomatic, may not be able to cope with the extra stress placed on the lacrimal system by wear of contact lenses. Possible mechanisms for a low tear volume include altered lacrimal production and evaporation. Intolerant patients did not have increased total protein concentrations that normally suggest dry eye/keratoconjunctivitis sicca (i.e., increased protein levels due to very low tear volume or increased residual inflammation).[53,54] However, the average tear flow rate of an intolerant subject was slower than that of the average tolerant contact lens wearer ($P < 0.06$) which may point to a reduced capacity to produce tears, but those tears that were produced were biochemically normal for two of the major regulated lacrimal proteins, lysozyme and lactoferrin,[12,36] and the major tear film immunoglobulins sIgA.

In a study published by our group,[55] we demonstrated that the concentration and activity of secretory phospholipase-A2 (sPLA2), the amount of oxidized lipid and the concentration of lipocalin in tears (another major regulated lacrimal gland protein)[12,36] were significantly different between contact lens–tolerant and –intolerant subjects. Fortunately, many of the same subjects enrolled in either group 1 or group 2 in the present study had been analyzed in the previous study.[55] This allowed for correlations to be sought between the clinical and biochemical variables in the present study and the lipid, sPLA2, and lipocalin concentrations and activity found in the previous study. Peroxidized lipid concentration was significantly correlated with meniscus height ($r = -0.580$; $P = 0.09$) and area ($r = -0.514$; $P = 0.024$), NI-TBUT (-0.585; $P = 0.009$), dry type ($r = 0.587$; $P = 0.008$), and tear flow rate ($r = -0.529$; $P = 0.02$). sPLA2 activity was correlated with NI-TBUT ($r = -0.463$; $P = 0.036$) and PRTT ($r = -0.458$; $P = 0.049$), whereas sPLA2 concentration was correlated with meniscus area ($r = -0.478$; $P = 0.033$) and tear flow rate ($r = -0.567$; $P = 0.009$). Lipocalin was significantly correlated with NI-TBUT only ($r = -0.440$; 0.036). Thus, it would appear that the tear film stability problems and relative lack of tear film volume in intolerant subjects are reflected in these tear film biochemical characteristics. Perhaps these lipid-associated variables disturb the structure of the tear film or reflect certain changes in lacrimal gland function.

Detailed analysis of the tear film clinical and protein characteristics and symptomatology of intolerant subjects enabled the development of four simple formulas for predicting lens intolerance based on a small number of variables. These formulas may be useful to help practitioners to diagnose patients before contact lens fitting. The initial specificity and sensitivity of the selected formulas was higher than would be expected by chance (>63%).[56] When the formulas were tested on a group of subjects being enrolled in a clinical trial of contact lens wear, the sensitivity of the test was maintained (i.e., no truly intolerant subjects were misclassified) but the specificity of the test was reduced (to ≤57%). This reduction in specificity means that, if the tests were used in clinical practice, certain tolerant subjects would have been classified as intolerant. It should be borne in mind that the criteria for entry into the clinical trial was that the clinicians should enroll subjects with a known history of contact lens tolerance and intolerance, which may introduce some bias. Prospective analysis of an unselected group of subjects using these preliminary findings is recommended. In addition, tolerance may depend on factors other than those measured in this study, including tear film biochemical variables such as lipocalin, sPLA2, or lipid peroxide concentration and activity; ocular topography; lid–cornea relationship; objective sensitivity of the ocular surface; and/or the patient's willingness to attempt contact lens wear. There is also some evidence that personality type and psychological factors influence both tolerance to lens wear (Erickson DB, et al. *IOVS* 2000;41:ARVO Abstract 4930) and reporting of symptoms.[57,58]

In summary, this study has demonstrated that clinical variables that may measure tear film volume and/or stability were related to intolerance during lens wear. This indicates that these intolerant subjects probably have tear film insufficiencies that preclude their use of contact lenses. Tear film protein concentrations measured in this study were not associated with contact lens intolerance, indicating that the concentration of lactoferrin, lysozyme, or total protein does not affect tolerance. Four formulas were designed and tested for their ability to predict contact lens intolerance. These had some value and predicted with excellent sensitivity whether subjects would be intolerant to contact lens wear.

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