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Title of Paper: Lax Eyelid Syndrome, Obstructive Sleep Apnea, and Ocular Surface Inflammation

IRB Status: ☑ Approved ☐ N/A

Type of Study: ☐ Basic science ☐ Case report, series ☐ Retrospective ☐ Prospective ☐ Randomized ☑ Controlled

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**TITLE:** *Lax Eyelid Syndrome, Obstructive Sleep Apnea, and Ocular Surface Inflammation*

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## ABSTRACT

**Purpose:** Lax eyelid syndrome (LES) is defined as the association of distensible "floppy" eyelids and chronic papillary conjunctivitis. "Floppy Eyelid Syndrome (FES)" has been reclassified as LES that occurs in young overweight men.[1] Eyelid histopathology in patients with LES demonstrates an overexpression of matrix metalloproteinase 9 (MMP-9), co-localized with elastin degradation, accounting for the "laxity". Alterations in normal elastin have also been reported in soft palate specimens from patients with OSA suggesting a potential systemic elastin dysfunction. The purpose of this study was: 1) establish the prevalence and degree of eyelid laxity in patients with newly diagnosed OSA; 2) assess MMP-9 in the tear film of patients with LES; and 3) document the correlation between the severity of several lax eyelid grading systems with a proposed "laxometer" device as well as the severity of sleep apnea.

**Methods:** 37 subjects underwent an eyelid laxity exam prior to polysomnography testing. The severity of sleep apnea was reported as a function of the apnea hypopnea index (AHI). The degree of eyelid laxity was determined using four methods: 1) degree of tarsal conjunctiva exposure on manual lid retraction; 2) duration of upper eyelid eversion while looking down; 3) degree of punctal excursion with lateral lid traction; and 4) measurement of eyelid distensability with the laxometer device. In addition to these examination tests, a commercially available MMP-9 tear film assay (InflammaDry®) was used to detect tear film MMP-9.

**Results:** 14 of 16 eyes (89%) with LES had a positive MMP-9 result ($p < .001$). There was a small but non-significant positive association between laxometer measurement and duration of eyelid eversion ($\tau = 0.16$, $p = .29$). Conversely, there was a small but non-significant negative association between laxometer measurement and duration of eyelid eversion ($\tau = -0.19$, $p = .25$). A nonparametric Kreskas-Wallis test was used to assess whether measurements of eyelid elasticity varied as a function of sleep apnea severity. Although the study was unpowered for statistical significance, a positive trend was found between degree of sleep apnea and eyelid

laxity as determined by laxometer measurements. There was also an association between the degree of conjunctival exposure and the severity of sleep apnea.

**Conclusion:** Elevated MMP-9 assays in this LES patient population suggests a potential role of MMP in the pathophysiology of chronic conjunctivitis and reactive ocular surface typically found in patients with lax eyelids. The eyelid laxity measurements suggest an association between the severity of LES and OSA severity that could have clinical relevance.

## INTRODUCTION:

The term "floppy eyelid syndrome" (FES) was first reported in 1981 to describe the association of rubbery, lax upper eyelids with tarsal papillary conjunctivitis seen in young obese men.[1] In 1994, Van den Bosch and Lemji expanded the classification system, to include three related conditions: 1) lax eyelid condition (LEC), describing patients with laxity of the eyelids only in patients of any age, and not necessarily obese; 2) lax eyelid syndrome (LES), in patients with LEC that also had chronic conjunctivitis; and 3) floppy eyelid syndrome (FES), in patients with LES that were also obese young men.[2, 3] Several studies have reported the association of FES with corneal and ocular surface disease.[4]

Obstructive sleep apnea (OSA) is a common disease that affects 20-25% of the adult population in the US. It is also a significant public health problem that is uniquely undiagnosed in 82% of patients and is responsible for $115 billion dollars in health care expenditures annually in the US.[5] We propose that ophthalmologists are critically positioned to identify this population at risk and refer them for a polysomnography.

OSA is characterized by interruption of ventilation for more than 10 seconds due to airway collapse.[6] This chronic hypoventilation places the individual at increased risk for significant systemic morbidity including cardiovascular (sudden cardiac death, arrhythmias) and ocular ischemic disease (normal tension glaucoma, ischemic optic neuropathy (ION), and retinal vascular occlusion).[6,7,8, 9, 10] Woog first reported the association of FES with OSA in 1990.[10] The association of LES (FES) and OSA has been reported in numerous other studies.[5, 12, 13, 14, 15, 16, 17] A positive correlation has also been reported between the severity of OSA and the severity of ocular surface disease.[18]

The pathophysiology of LEC has also not been clearly determined. Netland et al (1994) first reported a decrease in elastin content in the tarsal plate of patients with LES.[19] This observation was corroborated by Schlotzer-Schrehardt et al in 2005, who further demonstrated a co-localization of elastin loss with increased presence of matrix metalloproteinases, particularly matrix metalloproteinase-7 (MMP-7) and matrix metalloproteinase-9 (MMP-9), in the eyelids of affected individuals.[20] Interestingly, Sériès et al (2004) demonstrated elastin changes in soft palate specimens from OSA patients undergoing uvulopalatopharyngoplasty (UPPP).[21]

A potential systemic elastin dysregulation hypothesis is supported by Ryan et al (2005) who demonstrated selective activation of inflammatory cytokines in an in vitro model of intermittent hypoxia.[22] They further demonstrated that circulating tumor necrosis factor alpha (TNF-$\alpha$) levels were higher in OSA patients (2.56 pg/mL; IQR, 2.01 to 3.42 pg/mL) than in control subjects (1.25 pg/mL; IQR, 0.94 to 1.87; $P<0.001$) but normalized with continuous positive airway pressure (CPAP) therapy (1.24 pg/mL; IQR, 0.78 to 2.35 pg/mL; $P<0.002$).[22] Circulating neutrophil levels were also higher in OSA patients than in control subjects. Finally, Taban et al found elevated plasma leptin levels in patients with LES. They proposed that leptin might trigger the inflammatory cascade by up-regulating MMP-9, resulting in the breakdown of elastin.[23]

In our current study, we investigated the presence of MMP-9 in the tear film of patients with LES to determine the significance of its role in the pathophysiology of the disease. We also documented the presence and severity of LES in patients with mild, moderate, and severe OSA as determined by apnea-hypopnea index (AHI) on polysomnography. We tested several reported techniques for quantitating the severity of eyelid laxity as well as introduced a new method for grading eyelid laxity, the laxometer. We then determined if the severity of FES correlates with the severity of OSA.

## MATERIALS AND METHODS:

### Materials

This study introduces the "laxometer" device as a method for measuring eyelid laxity. It is a modified wire speculum that was developed with Katena instruments®. The laxometer was placed under the upper and lower eyelid to measure the distensability of the eyelids in millimeters using a constant spring-loaded force (Figure 1).

MMP-9 levels were obtained on each patient. Used in the evaluation of dry eye, the InflammaDry® assay kits, developed by RPS, detect the presence or absence of the MMP-9 enzyme in the patient's tear film. According to the product package insert, a cutoff study was performed to determine the concentration of MMP-9 required in solution to yield a "positive" result. A value of at least 40 ng/mL was established as a "positive" result. [24]

### Patient Evaluation and Data Collection

Patients were identified for participation in the study at the time of their initial sleep study appointment at the Loyola Pulmonology Sleep Center. Patients were referred to the Sleep Center for formal testing of sleep apnea. Those patients agreeing to participate in the study then underwent ocular examination consisting of visual acuity, color vision, pupil exam, intraocular pressure evaluation by tonopen, slit lamp anterior segment exam, and MMP-9 tear film assay.

At the same time, measurements of the degree of eyelid laxity were determined using three different reported methods in addition to our "laxometer" method: 1) degree of tarsal conjunctiva exposure associated with upper eyelid traction (Figures 2 and 3); 2) duration of upper eyelid eversion on downgaze following eyelid eversion; 3) degree of excursion of the lower punctum following lateral lower eyelid traction (Figure 4); and 4) vertical distensability of the eyelids as determined by the "laxometer"(Figure 5). Tarsal conjunctiva exposure was graded as described

by Acar et al.[18] Duration of upper eyelid eversion, as described by Beis et al, was measured in seconds while the eyes were in the inferior gaze position.[25] The third method of grading medial canthal tendon (MCTL) laxity was performed as described by Olver et al (Figure 4).[15] The horizontal position of the lower punctum was measured at rest and at lateral distraction with minimal pressure. Laxometer measurements were obtained as demonstrated in Figure 5.

Sleep study results were recorded, including the apnea-hypopnea index (AHI), which is defined as the number of episodes of apnea or hypopnea in a one hour sleep period.[6] OSA has been clinically defined as an AHI of greater than or equal to 5 in a person with excessive daytime sleepiness. The severity of OSA is graded into mild (AHI 5-14), moderate (AHI 15-30), and severe (AHI >31).[6]

Statistical Analysis

All data was recorded and stored in REDCap, a secure electronic research database. Statistical analysis was completed with the assistance of a biostatistician from the Loyola Clinical Research Office. A one-sample binomial test allowed us to evaluate whether the proportion of cases identified with LES that were MMP-9 positive differed from a hypothesized expected value of 14%, which was the previously cited amount of positive InflammaDry MMP-9 assays in mild dry eye syndrome.[26] A linear mixed effects model was used to assess whether each of the 4 eyelid elasticity measurements correlated with the degree of sleep apnea severity, whether an association existed between obesity or OSA and MMP-9 positivity in the tear film, and whether eyelid elasticity as measured by the laxometer correlated with other methods of grading eyelid laxity (MCTL, duration of eyelid eversion, and degree of tarsal conjunctiva exposure).

**RESULTS:**

Seventeen of 37 patients (46%) screened for OSA were determined to have LEC as defined by >1/3 tarsal conjunctiva exposure with upper eyelid traction. Of the 17 patients with LEC, 15 were determined to have a diagnosis of OSA (88.2%). Of the 37 total patients enrolled in this study, 2 patients did not have sleep study results available at the time of data analysis as they were lost to follow up. 32 of the remaining 35 patients were determined to have OSA (AHI > 5) (91.4%). Of these 32 patients, 15 (46.9%) had a tarsal conjunctiva exposure >1/3. These results are slightly lower than what was predicted by a study done by Acar et al., in which 164 out of 245 OSA patients (64.6%) were discovered to have a diagnosis of FES.[18]

Patients enrolled in our study were classified as having nonexistent, mild, moderate, or severe OSA based on their AHI. These four groups were collapsed into a binary set comprised of nonexistent or mild sleep apnea (N = 15) and moderate or severe sleep apnea (N = 20). Their laxometer measurements were compared. We found that as severity of sleep apnea increases, the degree of eyelid elasticity as measured by the laxometer also increased (Table 2). Patients with nonexistent or mild sleep apnea had a mean laxometer measurement of 24.23 mm (SE = 0.49) and those with moderate or severe sleep apnea had a mean laxometer measurement of 24.85 mm (SE = 0.44). While interesting, this correlation was not statistically significant (p = 0.36).

We compared degree of tarsal conjunctival exposure to OSA severity. Our results found that there was no meaningful association between sleep apnea severity and tarsal conjunctiva exposure ($p = 0.82$). Measurements of medial canthal tendon laxity were also compared to sleep apnea severity. Our results revealed no meaningful association between sleep apnea severity and medial canthal tendon laxity ($p = 0.38$). Finally, we compared duration of eyelid eversion to sleep apnea severity in our patients. Our results again revealed that there was no meaningful association between sleep apnea severity and eyelid eversion ($p = 0.40$).

This study also sought to compare previously established methods of grading eyelid laxity with our "laxometer" device. We found a small but nonsignificant association between the measurements of tarsal conjunctiva exposure and laxometer measurements (p=0.14). When there was less than 1/3 tarsal conjunctival exposure, the average laxometer measurement was 24.03 (SE = 0.43) millimeters. When the exposure was 1/3 to 2/3, the average laxometer measurement was 24.74 (SE = 0.59) millimeters. Lastly, when the exposure was greater than 2/3 the average laxometer measurement was 25.62 (SE = 0.66) millimeters (Table 3).

We also found a significant association between eyelid eversion time and laxometer measurements. For every one second increase in eyelid eversion, patients' laxometer readings were expected to increase by approximately 0.06 (95% CI: 0.01 – 0.12) millimeters ($p$ = .02) (Table 4).

For the medial canthal tendon laxity (MCTL) measurements, there was no significant association with the degree of eyelid elasticity as determined by the laxometer. These patients were arranged into 3 different groups: grades 0-I (N=20), grade II (N=31), or grades III-IV (N=23). The average laxometer measurements for MCTL grade 0-I was 24.39 mm (SE=0.57), 24.63 mm for grade II (SE=0.44), and 24.56 mm for grades III-IV (SE = 0.51).

Regarding the InflammaDry testing, the observed proportion of cases with positive MMP-9 assay in the LEC patients (75%) was significantly higher than the expected proportion (14%) identified by Schargus et al ($p$ < .001, Figure 6).[26] Finally, we did not find any significant association between MMP-9 tear film positivity and either sleep apnea (p=0.12) or obesity (p=0.96).

## DISCUSSION:

One of the most well-known systemic associations of LES is sleep apnea. Woog was the first to describe a relationship between OSA and LES in 1990.[11] In 1997, McNab described 17 patients with LES. Of those patients, 8 were referred for a sleep study and all were diagnosed with OSA.[27] Bouchard et al reported an association of LES of only 4% in 11,975 patients with OSA in a Loyola data mining study, suggesting that lax eyelid syndrome is underdiagnosed and its implications under-recognized.[28] However, the results of our study, as well as our clinical experience, suggest a much stronger association between OSA and LES. We found that 88.2% of patients with LEC who were evaluated for our study were diagnosed with OSA. Similar predictive findings were found in a study done by Muniesa et al. 45 patients diagnosed with FES were evaluated with an overnight sleep study. Of these patients, 38 (84.4%) were diagnosed with OSA. The prevalence of OSA in a population of patients with FES or, in our case, LES, far exceeds the prevalence of OSA in the general population (2-5%)[29]

In addition, Chambe et al. demonstrated that OSA was predictive of having FES, defined as papillary conjunctivitis with eyelid hyperlaxity. Their study showed that FES present in only 15.8% of patients without a diagnosis of OSA, while 25.8% of patients with a diagnosis of OSA met the diagnostic criteria for FES.[13]

OSA is a significant cause of both ocular and systemic morbidity and mortality.[8, 9, 10] Hypoventilation and subsequent chronic intermittent hypoxemia as a consequence of this disease predisposes these individuals to cardiovascular disease, congestive heart failure, pulmonary hypertension, stroke, and many other life threatening illnesses.[6, 7] These effects may be a result of the systemic low grade inflammation as measured by peripheral blood TNF alpha, IL-1, neutrophil count.[30] LES has also been found to be associated with additional systemic manifestations including hypertension, diabetes mellitus, and ischemic heart disease.[6, 7]

According to a 2010 report by the Harvard Medical School Division of Sleep Medicine, the prevalence of moderate to severe sleep apnea in the US was about 25 million patients with 82% of patients (19 million) undiagnosed. The total cost for managing sleep apnea, and its comorbidities was discovered to be on the order of $100 billion annually.[5] The high association of LES and OSA reported in our study will help the eye care community to gain better awareness and seek appropriate referral for a sleep study.

Additionally, 75% of the patients in this study with LES had positive tear film MMP-9 assays. MMP-9 is a well-known inflammatory marker present in patients with dry eye syndrome. The statistically significant ($p<.001$) positive association between MMP-9 and LES strongly supports the role of MMP-9 in the pathophysiology of the disease. It also suggests an explanation as to why ocular surface diseases such as dry eye syndrome, phlyctenular disease, superior limbic keratoconjunctivitis, neurotrophic keratitis, and many other non-infectious ocular inflammatory diseases are also found in these patients.[4]

This study also sought to standardize a method of grading eyelid laxity and to compare severity of eyelid laxity with the severity of sleep apnea. We found a small but nonsignificant association between laxometer measurements and severity of sleep apnea ($p = 0.26$). Previously described measurements of eyelid laxity, including degree of tarsal conjunctival exposure, laxity of the medial canthal tendon, and eyelid eversion are commonly employed by ophthalmologists in practice today to diagnose LEC. In our evaluation, the severity of eyelid laxity, as described by these methods, was proven to be a poor predictor of OSA severity. These methods of grading eyelid laxity are highly subjective and difficult to reproduce. While not statistically significant, the laxometer measurements obtained in this study were shown to be better predictors of OSA severity.

Additionally, this study sought to compare our proposed laxometer device with other previously described methods of grading LEC. The only statistically significant association was found between the laxometer and the eyelid eversion time ($p=0.02$); no significant association was found between the other methods.

In summary, there is a strong predictive value of OSA in patients with LEC. OSA causes significant systemic inflammatory disease associated with elevation of inflammatory markers in the peripheral blood (TNF-alpha, IL-1) and on the ocular surface (MMP-9).[22] This inflammation is potentially associated with elevated rates of elastin degradation in soft tissues, including those in the soft palate and the eyelids. OSA is undiagnosed in 80% of patients and, without treatment, this cycle is potentiated, leading to increased morbidity and mortality. Making the diagnosis of LEC in the ophthalmology clinic provides a significant opportunity to identify patients at risk for OSA. For this reason, the ophthalmologist plays a key role in addressing this critical public health problem.

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**FIGURES AND LEGENDS:**

**Table One:** Acar et al[22]

| Clinical Finding | No OSA | Mild OSA | Mod. OSA | Severe OSA | Sig (p<.05) |
|---|---|---|---|---|---|
| **FES** | 23.1% | 41.7% | 66.7% | 74.6% | p<0.01 |
| **OSDI** | 12.57 +/- 17.64 | 22.90 +/- 16.78 | 45.94 +/- 22.03 | 56.68 +/- 22.5 | p<0.01 |
| **Schirmer (mm)** | 10.76 +/- 3.58 | 9.83 +/- 2.53 | 7.73 +/- 2.42 | 6.97 +/- 2.15 | p<0.01 |
| **TBUT (sec)** | 10.53 +/- 3.64 | 9.46 +/-2.40 | 7.29 +/-2.13 | 6.82 +/-2.20 | p<0.01 |
| **Corneal Stain** | 0.26 +/- 0.60 | 0.40 +/- 0.71 | 0.98 +/- 0.72 | 1.14 +/- 0.90 | P<0.01 |

**Figure One:** The Laxometer device

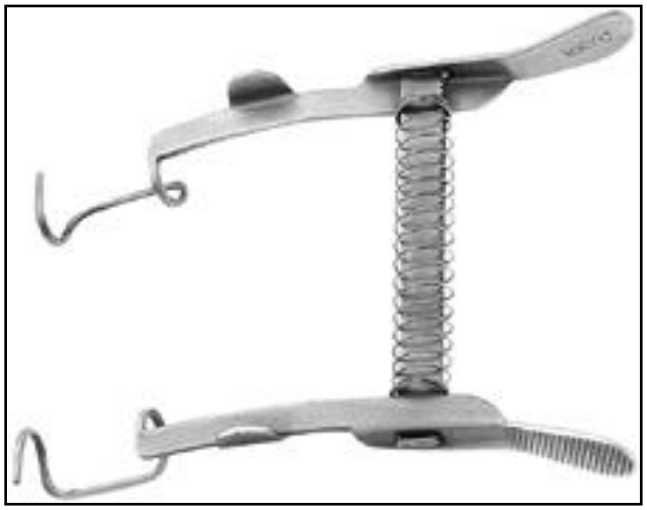


**Figure Two:** Severe tarsal conjunctival exposure upon lateral upper eyelid lateral traction.[22]

**Figure Three:** Grading system established by Liu et al: Grade 0 (normal): no tarsal conjunctiva visible (A); Grade 1 (mild): <1/3 of upper tarsal conjunctiva visible (B); Grade 2 (moderate): 1/3 to ½ of upper tarsal conjunctiva visible (C); Grade 3 (severe): > 1/2 of the upper tarsal conjunctiva visible (D).[31]

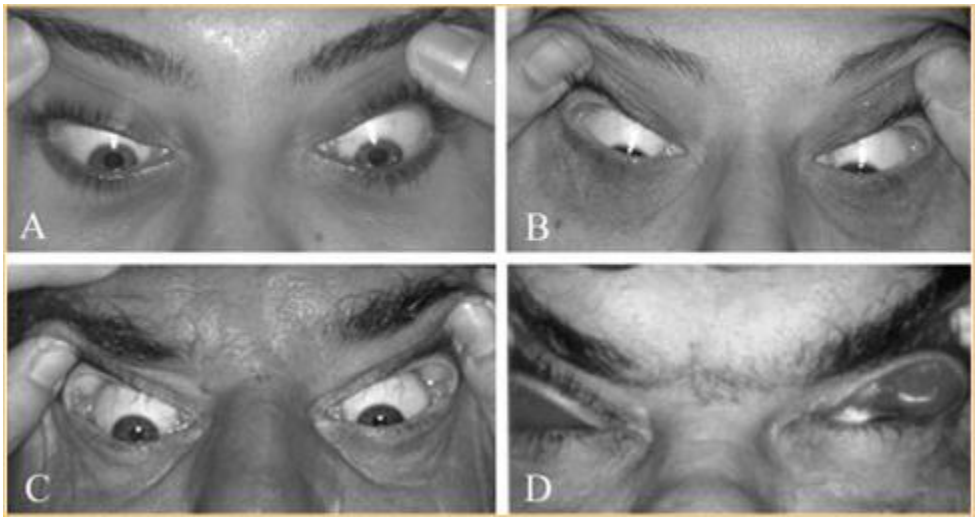
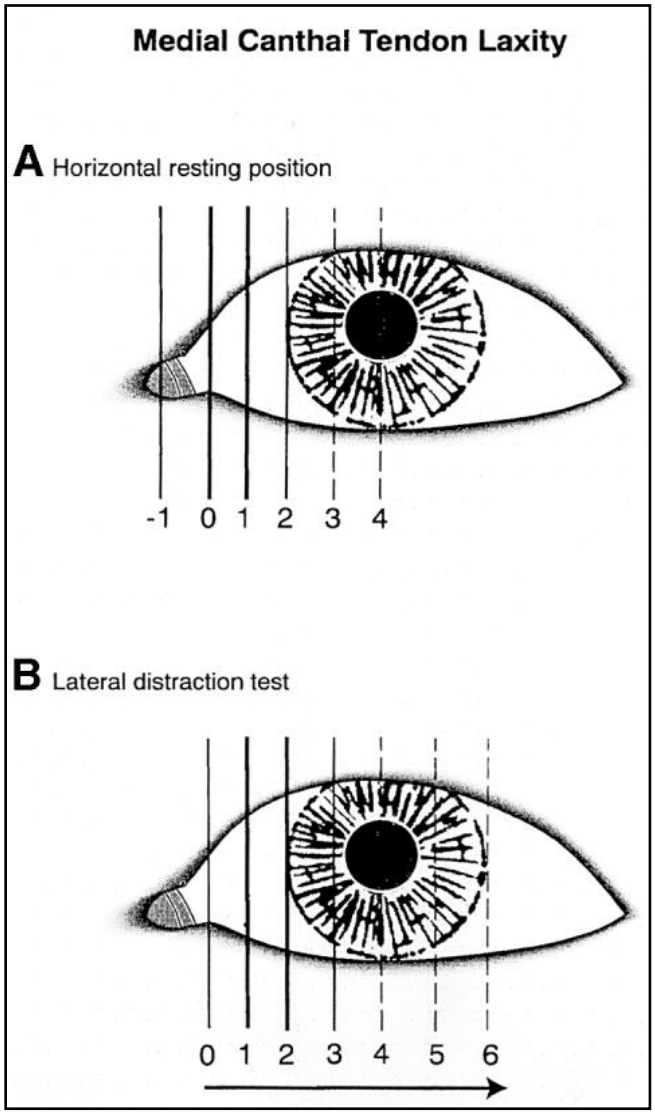


**Figure Four:** Measuring degree of medial canthal tendon laxity as described by Olver et al.[21]



346 **Figure Five**: Eyelid distensibility as measured by the proposed laxometer introduced in this study. The

347 distensibility was measured in millimeters as the distance between the upper and lower speculum bars.

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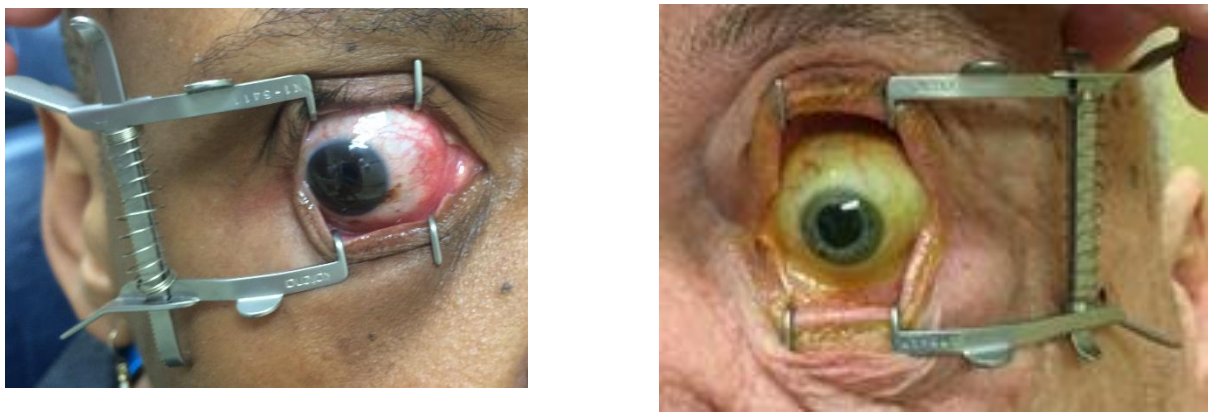

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**Figure Six**: N = 16/17 patients with Floppy eyelid syndrome had a valid MMP-9 assay value recorded. Among these patients, the observed proportion of cases with a positive MMP-9 assay (75%) was significantly higher than the expected proportion of 14%, which is the rate of positive MMP-9 assay in mild dry eye patients as described by Schargus et al ($z$ = 7.03, exact $p$ < .001).[35]

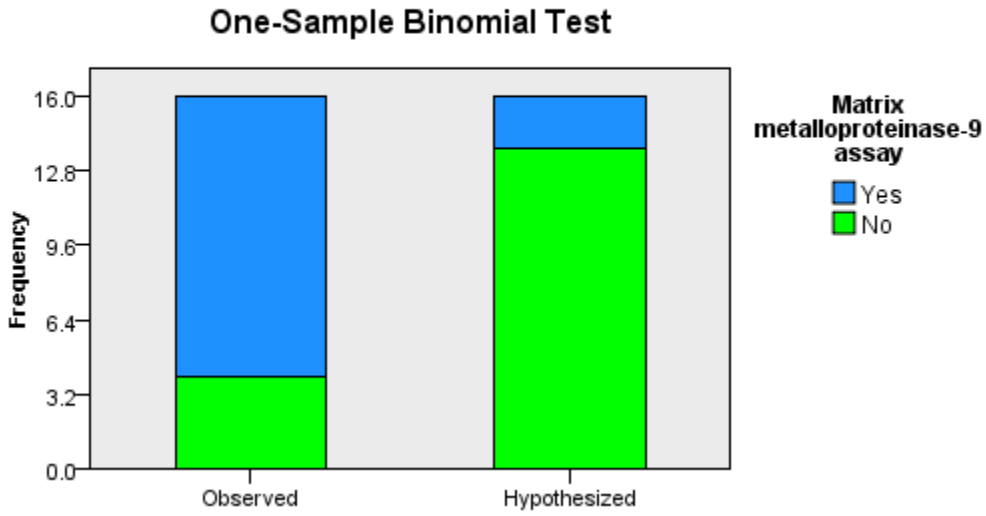

**Table Two:** *Eyelid elasticity as a function of sleep apnea severity*

| Sleep Apnea Severity | Laxometer Mean Difference (mm) | 95% Confidence Interval | | *p* |
|---|---|---|---|---|
| | | Lower | Upper | |
| **Moderate/Severe vs Nonexistent/Mild** | 0.6177 | -0.7287 | 1.9642 | .36 |
| ***Note***: Valid N = 35 | | | | |

Patients with nonexistent or mild sleep apnea had a mean laxometer measurement of 24.23mm (SE = 0.49) and those with moderate or severe sleep apnea had a mean laxometer measurement of 24.85 (SE = 0.44). There was no difference between these two groups in their mean laxometer measurement ($M_{DIFF}$ = 0.62, 95% CI: -0.73 – 1.96; *p* = .36).

I would add the other 3 measures of lid laxity and correlate these measures with the severity of sleep apnea

**Table Three:** *Eyelid elasticity as a function of tarsal conjunctival exposure*

| Tarsal Conjunctival Exposure Comparison | | Laxometer Mean Difference (mm) | 95% Confidence Interval | | *p* |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| **One third to two thirds** | **Less than one third** | 0.7131 | -0.7704 | 2.1966 | .71 |
| **Greater than two thirds** | **Less than one third** | 1.5894 | 0.003030 | 3.1758 | .0496 |
| **Greater than two thirds** | **One third to two thirds** | 0.8763 | -0.8240 | 2.5766 | .31 |
| ***Note***: Valid N = 37. Overall model significance $p$ = .14 | | | | | |

Overall, there was no significant association between tarsal conjunctival exposure and laxometer readings ($p$ = .14). However, compared to when the tarsal conjunctival exposure was less than 1/3, laxometer measurements were noticeably higher when the tarsal conjunctival exceeded 2/3 exposure ($M_{DIFF}$ = 1.59mm, 95% CI: 0.003 – 3.18; $p$ = .0496).

372 **Table Four**: *Association between eyelid eversion and eyelid elasticity*

| | β | 95% Confidence Interval | | *p* |
|---|---|---|---|---|
| | | Lower | Upper | |
| **Eyelid Eversion (per 1 second increase)** | 0.06244 | 0.008531 | 0.1163 | .02 |
| ***Note***: Valid N = 36 | | | | |

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374 For every one second increase in eyelid eversion, patients' laxometer readings were expected to
375 increase by approximately 0.06 (95% CI: 0.01 – 0.12) millimeters (*p* = .02).

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