

# Effect of thermal pulsation treatment on tear film parameters in dry eye disease patients

Michelle J Kim  
Sandra S Stinnett  
Preeya K Gupta

Department of Ophthalmology, Duke  
University Eye Center, Durham,  
NC, USA

**Purpose:** The goal of this study was to evaluate the effect of thermal pulsation treatment on tear film parameters, specifically osmolarity and matrix metalloproteinase-9 (MMP-9), in patients with meibomian gland dysfunction (MGD) and dry eye disease (DED).

**Methods:** A single-center review of 189 eyes that underwent thermal pulsation treatment was performed. Data were collected on pre and posttreatment osmolarity, MMP-9, tear break-up time (TBUT), and ocular surface disease index (OSDI) score. Statistical analyses were performed to detect any significant differences after treatment.

**Results:** Thermal pulsation treatment led to significant improvements in TBUT (mean increase from 4.5 to 8.5 seconds [ $P<0.001$ ]), OSDI score (mean decrease from 50.5 to 41.6 [ $P=0.024$ ]), and MMP-9 (50% positive rate pretreatment compared to 26% positive rate post treatment [ $P<0.0001$ ]). In the subset of patients who had a baseline osmolarity  $>307$  mOsm/L (ie, diagnostic for DED), there was a significant improvement in the mean tear osmolarity from 317.1 to 306.6 mOsm/L after treatment ( $P=0.002$ ).

**Conclusion:** Treating MGD is an important component of caring for the DED patient. Thermal pulsation treatment can improve MMP-9 levels on the ocular surface of patients with MGD and DED, as well as improve osmolarity in those with abnormal initial values. The present study suggests that meibomian glands play an important role in tear film dynamics and, as such, effective therapy such as thermal pulsation treatment aimed at improving meibomian gland health, can aid the restoration of normal tear film parameters and decrease patient symptoms of DED and MGD.

**Keywords:** thermal pulsation, dry eye disease, meibomian gland dysfunction, osmolarity, matrix metalloproteinase-9

## Introduction

Meibomian gland dysfunction (MGD) has been identified as a major cause of dry eye disease (DED), leading to tear film instability and ocular surface inflammation.<sup>1</sup> Traditional therapies such as eyelid hygiene, hot compresses, and omega-3 supplementation had been the mainstay of treatment until thermal pulsation emerged as a promising therapy for evaporative DED and MGD. A single 12-minute treatment with the Lipiflow thermal pulsation device (Tear Science, Morrisville, NC, USA) has been shown to be effective and superior to conventional therapy with warm compresses.<sup>2-4</sup> The treatment effect is generally gradual, but some have reported improvement as early as 2 weeks.<sup>4</sup> Prior studies have shown the treatment effect can be sustained for 1 year,<sup>2,5,6</sup> with relief in some parameters lasting up to 3 years.<sup>7</sup>

Previous investigations of thermal pulsation have assessed measures of DED such as tear break-up time (TBUT), ocular surface disease index (OSDI), standard patient evaluation of eye dryness (SPEED), meibomian gland function/expression, corneal

Correspondence: Preeya K Gupta  
Department of Ophthalmology,  
Duke University Eye Center, 4709  
Creekstone Drive, Suite 100,  
Durham, NC 27703, USA  
Tel +1 919 660 5234  
Fax +1 919 660 5070  
Email preeya.gupta@duke.edu

and conjunctival staining, Schirmer test, tear osmolarity, tear meniscus height, and lipid layer thickness.<sup>2-4</sup> Of these variables, significant improvements have been reported with dry eye symptoms, meibomian gland function, and TBUT posttreatment.<sup>2-4</sup> There is little known about the effect of thermal pulsation treatment on ocular surface inflammation and osmolarity. DED can be complex and multifactorial in nature, and an understanding of what impacts the presence or absence of inflammation is of great value to the clinician. The primary goal of the study is to report the effect of thermal pulsation treatment on matrix metalloproteinase-9 (MMP-9) levels and osmolarity of the tear film. Secondly, the study will report clinical outcomes of the thermal pulsation treatment.

## Methods

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Duke University Hospital Institutional Review Board (IRB). A retrospective chart review was performed on all patients undergoing a single Lipiflow thermal pulsation treatment between December 2013 and April 2016 at the Duke University Eye Center by one physician (PKG). Due to the retrospective nature of the study, a waiver of consent was granted by the IRB for review of medical records. All data were collected and stored on secure servers to maintain patient data confidentiality.

Demographic data were collected from the initial evaluation including the patient's age, sex, and treatment eye. Pretreatment and posttreatment clinical data were recorded, including TBUT, osmolarity as measured by the TearLab Osmolarity System (TearLab Corporation, San Diego, CA, USA), MMP-9 assay as measured by Inflammadry (Rapid Pathogen Screening, Sarasota, FL, USA), and OSDI score. All standard protocols, as specified by the manufacturer, were observed for osmolarity and MMP-9 testing. According to the manufacturer, the MMP-9 test displays as positive when the detected level is  $>40$  ng/mL.<sup>8</sup> Posttreatment data were

collected from the first subsequent clinic visit following treatment. Patients included did not initiate any new therapy after or concomitant to thermal pulsation treatment. If over-the-counter treatments for MGD and DED (such as artificial tears, warm compresses, eyelid scrubs, omega 3 supplementation) were part of the patient's typical routine prior to treatment, they continued this after thermal pulsation treatment, and no new regimen was encouraged. Statistical analyses were performed using a paired *t*-test with generalized estimating equations to account for correlation between the two eyes of the same patient. The McNemar's test was used to compare categorical variables such as MMP-9.

## Results

During the study period, 189 eyes of 98 patients were treated with thermal pulsation. The average age was 59.8 years (median 64 years, range 18–82 years). The majority of patients (81.6%) were female. In 77 patients (78.6%), the initial evaluation took place on the same day as the treatment. For the remainder of the 21 patients, there was an average of 53 days (median 31 days) between evaluation and treatment. There was an average of 77 days from treatment to follow-up (median 64 days), during which posttreatment measurements were taken.

When including all patients in the study, tear osmolarity improved from an average of 303.3 mOsm/L before treatment to 302.8 mOsm/L after treatment, a difference that was not statistically significant ( $P=0.763$ ; Table 1). However, it is important to note that not all patients prior to the treatment had an abnormal osmolarity. In the subset of patients who had a baseline osmolarity  $>307$  mOsm/L (ie, diagnostic for DED), there was a significant improvement in the mean tear osmolarity from 317.1 to 306.6 mOsm/L after treatment ( $P=0.002$ ). When also including patients with an inter-eye difference of  $>7$  mOsm/L (also diagnostic for DED), there was still a significant improvement in the mean tear osmolarity from 309.7 to 304.1 mOsm/L after treatment ( $P=0.026$ ). The average pretreatment TBUT was 4.5 seconds, which improved

**Table 1** Effect of thermal pulsation on objective tear film parameters and symptoms of dry eye disease

Variable	Number of eyes	Pretreatment, mean (SD)	Posttreatment, mean (SD)	P-value
Osmolarity (mOsm/L)	106	303.3 (12.9)	302.8 (16.43)	0.763
Baseline $>307$	39	317.10 (8.1)	306.59 (19.52)	<b>0.002</b>
Baseline $>307$ or $>7$ difference	58	309.71 (13.1)	304.10 (16.92)	<b>0.026</b>
Tear break-up time(s)	164	4.53 (1.4)	8.50 (1.73)	<b>&lt;0.001</b>
Ocular surface disease index	81	50.48 (25.1)	41.35 (26.44)	<b>0.024</b>
Matrix metalloproteinase-9 assay	114	57/114 positive	30/114 positive	<b>&lt;0.0001</b>

**Note:** Bold values are statistically significant.

to 8.5 seconds after treatment ( $P<0.001$ ). The mean OSDI score decreased from 50.5 pretreatment to 41.6 posttreatment ( $P=0.024$ ). The MMP-9 assay was positive in 57 of 114 eyes, or 50% of eyes, before treatment compared to 30 of 114 eyes, or 26% of eyes, after treatment ( $P<0.0001$ ).

## Discussion

This study shows that thermal pulsation treatment improves tear film parameters, including MMP-9 levels and osmolarity in DED and MGD patients. This information highlights that meibomian gland health is critical to minimizing inflammation on the ocular surface. MMP-9 is a proteolytic enzyme produced during the inflammatory cascade by ocular surface cells in response to desiccating stress.<sup>9</sup> This stress can then lead to alterations in the corneal epithelial barrier. MMP-9 is present in higher levels in patients with DED, including MGD.<sup>9</sup> MMP-9 levels are useful markers to follow treatment because they correlate with other measures of DED such as OSDI, TBUT, meibomian gland function,<sup>10</sup> low-contrast visual acuity, fluorescein staining, topographic surface regularity index, and health of the corneal epithelium on confocal microscopy.<sup>11</sup> After thermal pulsation in this study, the number of patients with a positive MMP-9 test decreased by ~50%. To the best of the authors' knowledge, this is the first time that a study has investigated the effect of thermal pulsation treatment on ocular surface MMP-9 levels.

This information has clinical relevance as this study shows that there is a high rate of elevated MMP-9 levels in patients with MGD and DED, further supporting the need for clinicians to screen patients for ocular surface inflammation. This study also gives clinicians a greater understanding of how thermal pulsation treatment impacts tear film chemistry, which is an important part of managing MGD and DED. Extrapolating from this information, one can presume that when treating patients with ocular surface inflammation, it is important to treat any signs of MGD. The mechanism of action of thermal pulsation has been primarily thought to be a mechanical relief of meibomian gland obstruction. The present data suggest that relieving the obstruction may have a downstream effect on tear chemistry and ocular surface inflammation as well.

Similar to prior studies, in this study also, it was found that thermal pulsation treatment also improves TBUT and OSDI scores.<sup>2-4</sup> Also, as in previous studies, there was no significant change in mean osmolarity when looking at the study group as an aggregate.<sup>3,12</sup> However, the authors felt it was important to analyze the subgroup of patients who had

elevated osmolarity or an inter-eye difference  $>7$  mOsm/L prior to treatment, as these patients represent those who meet the diagnostic criteria for DED specifically. The cutoff for defining abnormal osmolarity was determined by the manufacturer who specifies that osmolarity value  $\geq 308$  mOsm/L is indicative of DED.<sup>13</sup> Furthermore, according to a study by Versura et al that compared osmolarity to other measures of DED, a value over  $\sim 307$  mOsm/L corresponds to moderate or severe dry eye.<sup>14</sup> Therefore, subgroup analysis was performed on patients with a baseline osmolarity of  $>307$  mOsm/L and yielded a statistically significant improvement from an average of 317.1 to 306.6 mOsm/L. This suggests that by osmolarity standards, thermal pulsation can reduce moderate or severe dry eye to a milder disease state.

Tear hyperosmolarity plays a significant role in the pathophysiology of DED by promoting the induction of inflammatory mediators, which then causes apoptosis, goblet cell loss, decreased mucin production, and tear film instability – all of which then further escalate the cycle of hyperosmolarity.<sup>15</sup> In addition, hyperosmolarity has been demonstrated to cause damage to corneal nerves, thereby decreasing the corneal sensitivity necessary to regulate proper tear production.<sup>16</sup> However, with early treatment, corneal nerve function may recover,<sup>16</sup> further highlighting the importance of timely diagnosis and treatment of hyperosmolarity.

Due to the retrospective nature of the study, there are some limitations to this study. First, all patients included in the study represent those presenting to a tertiary care center. Many had tried and failed prior treatments, which may not be generalizable to all populations. Second, there were differential follow-up times, which could make the data susceptible to mean regression. Despite the range in follow-up times, these data points were included in the statistical analysis because they are still within the potential efficacy time frame of thermal pulsation.<sup>2,4</sup> Next, there was no opportunity to measure patients serially to determine what exact time points the treatment led to improved tear film inflammation and osmolarity. Future studies may elucidate more precisely when and by how much MMP-9 levels and osmolarity levels change and at what time point. Last, it was not possible to include a placebo group because of the retrospective nature. In the future, a randomized trial with a placebo group, which could include a sham treatment, may allow for more direct comparison to validate the findings of this study.

## Conclusion

Overall, thermal pulsation is an effective treatment that leads to significant improvements in both subjective and objective

measures of DED, including TBUT, OSDI, osmolarity in moderate or severe DED, and MMP-9 levels. MMP-9 is a newer objective test that can be used to follow treatment effect in DED patients. Treating the meibomian glands with thermal pulsation can improve inflammation, and clinicians should be more aware of diagnosing MGD as well as having a low threshold to treat it, especially in patients with elevated MMP-9 and osmolarity levels.

## Disclosure

PKG is a consultant to Tear Science, Tear Lab, Shire, Allergan, AMO, Alcon, BioTissue. The other authors report no conflicts of interest in this work.

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