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Editorial

Luo and Colleagues Turn the Lights Back on . . . on Dry Eye

[1]In 1940, Sjögren took conjunctival biopsies from the patients with the syndrome that would bear his name, prepared them on microscope slides, and examined them under his light microscope and concluded that it appeared as if some "force" was pulling water across the ocular surface.[1,2] A year later, Von Bahr suggested that tear film osmolarity would be a function of rate of tear secretion and evaporation, and the decreased tear secretion or increased evaporation would lead to increased tear film osmolarity.[3] In 1952, Balik examined the histopathology of dry eye and concluded that the changes could be attributed to "increased sodium chloride" in the tear film.[4] In 1970 Mishima and his group, with great difficulty, were able to measure the osmolarity of tear microvolumes in six dry eyes and demonstrate an elevation of about 25 mOsm/L.[5] In 1978, our research group developed a non-invasive method to collect microvolume tear samples from patients, avoiding the classic problems of reflex tearing and sample evaporation, and in the first large series, was able to document clearly that patients with dry eye had elevated tear film osmolarity.[6] Others at the time were postulating that ocular surface changes were not due to the change in tear film osmolarity but, rather, were due to a primary inflammatory attack on the ocular surface, while others were attributing the changes to dry spot formation. Yet in the 1940s, Sjögren had found that epiphora patients who had their lacrimal glands removed had the same ocular surface histopathology as Sjögren's patients,[1] ruling out the need to invoke an inflammatory disease process unrelated to decreased tear production, or increased evaporation for that matter. The "dry spot" hypothesis became untenable when Lemp reported that about half of his dry eye patients had sufficient tear film stability to avoid tear film breakup between blinks.[7]

Our laboratory group subsequently demonstrated that the development of dry eye is dependent on and proportional to an elevation of tear film osmolarity, fulfilling the equivalent of Koch's Postulates in showing that elevated tear film osmolarity can directly cause and promote the development of dry eye ocular surface disease.[8-17]

Then some very red and inflamed eyes, with "canine dry eye," became less red and inflamed when treated with topical anti-inflammatory therapies, and for a while the waters became muddied, and the air became dark and foggy. Read the package insert for one of these products and one finds that it has shown no efficacy in relieving patient symptoms, and no beneficial effect to the ocular surface.

In the current issue of The Journal, however, the important paper by Drs. Luo, Li, Corrale and Plugfelder demonstrates that hyperosmolarity, by itself, "stimulates expression and production of IL-1b, TNF-a and MMP-9 on the ocular surface" in an in vivo animal model, and that these pro-inflammatory cytokines in turn activate the mitogen activated protein kinase cascades. In a recent ARVO paper, Berra confirms and takes this finding even further by showing in a normal human conjunctiva cell line, and in patients with Sjogren's syndrome dry eye and non-Sjogren's syndrome dry eye, that hyperosmolarity causes this increase in ocular surface proinflammatory cytokine production in conjunctival *epithelium* by nuclear translocation (movement from the cytoplasm to the nucleus) of the transcription factor Nuclear Factor kappa-betta (NF-kb). Moreover, he shows in dry eye patients that the nuclear translocation of NF-kb in their conjunctiva is proportional to the increase in tear film osmolarity.[21] In plain language—when you damage the ocular surface with increased tear film osmolarity, or if you damage the eye surface by direct mechanical trauma, you get inflammation.

Elevated tear film osmolarity causes the symptoms and signs of dry eye, whether the increase results from decreased tear production or increased evaporation, and thus when one treats dry eye with methods that reduce elevated tear film osmolarity—a hypotonic electrolyte-balanced lubricant eye drop,[18,19] punctal occlusion,[20] moist chambers, and, in severe cases, tarsorrhaphy, one improves patient symptoms and reduces ocular surface staining. Let's go about the work of developing still better ways to lower elevated tear film osmolarity so that every dry eye patient can find complete dry-eye relief. Congratulations to Dr. Luo and colleagues for turning the lights back on.

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