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Estimating basal tear osmolarity in normal and dry eye subjects☆

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ABSTRACT

Purpose: Tear osmolarity (tOsm) is used as a measure of severity in dry eye disease (DED) and has been proposed as an index of body hydration. In DED the level of tear hyperosmolarity is compared with that of a control population. It is proposed here that a better index of body hydration and a more valid reference point in DED can be acquired by measuring the tOsm after a period of evaporative suppression.

Method: 8 normal and DED subjects were recruited, their tOsm measured in uncontrolled environmental 'clinic conditions'. Then in experiment 1 they entered a controlled environment chamber and had tOsm measured after 45 minutes of eye closure and then, with the eyes open, at 15 minute intervals for a further 45 minutes, at a relative humidity (RH) of 45%. Alternatively, in experiment 2, they had tOsm measured every 15 minutes for 45 minutes during exposure to 70% RH, as a separate measure to suppress evaporation.

Results: A significant decrease in tOsm occurred in both normal and DED subjects after lid closure in experiment 1 (normal RE $p = 0.015$; normal LE $p = 0.006$; DED RE $p = 0.0002$; DED LE $p = 0.01$). The tOsm also fell slightly after exposure to 70% RH in experiment 2 significant in the LE of normal group only (normal LE $p = 0.045$).

Conclusions: Suppression of tear evaporation resulted in a fall in tOsm, close to that of plasma osmolarity (285–295 mOsm/L). It is proposed that this new measure, termed Basal Tear Osmolarity (BTO), could provide a valuable index of plasma osmolarity and hence of body hydration and in DED, a personal baseline against which to gauge the severity of tear hyperosmolarity.

1. Introduction

Tear hyperosmolarity has been recognised as the central mechanism of dry eye disease (DED) for some decades [1–3], responsible both directly and by initiating a chain of inflammatory events, for the ocular surface damage of DED [4–6]. Tear osmolarity (tOsm) is considered to be the best single diagnostic test for DED [7,8]. A meta-analysis of data from several studies, gives the average tear osmolarity in normal adults as 302 ± 9.7 mOsm/L [9] with similar values reported by Sullivan et al. [10] (302.2 ± 8.3 mOsm/L) and Jacobi et al. [11] (301 mOsm/L, range 298–304) based on use of the TearLab® osmometer alone. A tOsm of 308 mOsm/L is considered to be the most sensitive threshold to distinguish normal from mild/moderate forms of DED and 315 mOsm/L the most specific cut off [7]. Currently the progression or status of DED in an individual is measured against values derived from population norms, generated from subjects of both sexes and representing individuals over a wide age range.

The nomenclature used to describe solute concentration in the tears and plasma is not the same. The term *osmolarity* is used in reference to tears and is the number of osmoles of solute per litre of solution (mOsm/L). When referring to plasma the term *osmolality* is used and denotes the number of osmoles per kilogram of solution (mOsm/kg). The term osmolarity is also used with reference to serum or plasma when the value is determined by a calculation, based on composition [12]. Clinically the numerical difference between the two terms is small and of no practical importance. Here we use either term, according to its literature source.

Measurement of tear osmolarity has also been advocated as a means to detect body dehydration. Recently, Fortes et al. [12] reported a positive relationship between whole body hydration, measured as plasma osmolality (pOsm) and tOsm, in a group of young adults during a period of imposed systemic dehydration and during restoration to euhydration. The term *osmolarity*, used with reference to tears, is the number of osmoles of solute per litre of solution (mOsm/L), while *osmolality* denotes the number of osmoles per kilogram of solution (mOsm/kg).

The experiment involved three bouts of exercise cycling on a

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stationary ergometer in a controlled environmental chamber (CEC) set to 33 °C and 50% RH to induce dehydration, where the subjects either (i) received no fluid throughout the exercise bouts or (ii) received a volume of water sufficient to offset that lost through sweating. Each consecutive bout of exercise was designed to result in a 1%, 2% or 3% loss in body mass. After each bout, and in both phases of the experiment, the subject exited the CEC and had tOsm measured using the TearLab® device, in open eye conditions, along with body mass, urine and blood samples. In this study, plasma osmolality, urine specific gravity and tOsm increased with progressive dehydration and were restored by rehydration, to pre-exercise levels. The mean correlation between tOsm and pOsm was r = 0.93, and that between USG and pOsm was r = 0.72 the authors proposed the measurement of tOsm as a surrogate for pOsm, in the rapid detection of dehydration in sports medicine, in infants [13] and in the elderly.

Dehydration in the elderly is associated with a considerable morbidity and mortality [14,15] and the condition is underdiagnosed in care-home residents [16] and the elderly population generally. Plasma osmolality is the standard measurement of systemic dehydration against which other methods are compared [17] and there is some attraction in the possibility of diagnosing dehydration using a simple, reliable, bedside test [18,19]. Fortes et al. [12] using a tOsm reference value of 310 mOsm/L estimated a sensitivity of 80% and a specificity of 92% using this approach for the detection of suboptimal hydration.

An early study by Krogh et al. [21] reported that tOsm was 'similar' to that of serum in a small group of subjects (308 mOsm/L in tears versus 294.32 mOsm/L in serum) and concluded that the osmolarities of these two fluids might actually be the same, the higher tear value (which would nowadays be regarded as indicative of DED), being dependent on evaporation during processing of the tears. It is now accepted that tOsm measured in open eye conditions exceeds that of secreted tears, as a result of evaporation from the tear film. Terry and Hill [20], reported the average daytime tOsm in 6 young adults to be 310 ± 5.7 mOsm/kg (range 299–323 mOsm/kg), these values again overlapping those currently associated with DED. This compared to a tOsm of 285 ± 2.4 mOsm/kg (range 282–288 mOsm/kg), measured immediately after a 6–8 h period of eye closure (i.e. sleep). The closed eye values showed less variability and it is of interest that they fell within values reported for pOsm – 285–295 mOsm/kg in normally hydrated subjects consuming > 3.0 l fluid each day [18,21,22]. Thomas et al. [23] cite a broader range for serum osmolality of 275 to < 295 mOsmol/kg. A similar difference between post-sleep and waking tOsm was reported by Niimi et al. [24] who found tears to be significantly hypo-osmotic after a period of sleep, 264 ± 14 mOsm/L, compared with the pre-sleep value of 297 ± 15 mOsm/L. Thereafter, tOsm rose quickly in the first 10 min after eye opening and reached the baseline level within 40 min of waking. There was a relatively hyperosmotic trend toward the end of the day. The very low, post sleep, tOsm value, far below that expected of plasma, was not remarked upon.

In DED, evaporation causes a rise in tOsm, either because evaporation occurs from a reduced volume of tears, as in aqueous-deficient dry eye (ADDE) or because there is an abnormally high evaporation rate, as in evaporative dry eye (EDE) [4,25,26]. This forms the basis of treatments using moisture-conserving goggles [27–29] where exposure to an environment of 100% relative humidity (RH), like eye closure, results in a total suppression of tear evaporation.

To understand the effect of eye closure on tOsm it is necessary to consider the osmolarity of the tear secretions that go to make up the tears, at their site of production. The watery component of the tears derives chiefly from the lacrimal gland (main and accessory), supplemented by secretions from the conjunctiva and cornea. The tears are mixed and distributed by blinking [30–32] and eye movements [33]. Total tear volume has been estimated to be in the region of 7 µl and tear turnover 1.10 µl/min [34].

The osmolarity of the tears is mainly dependent on its ionic content and that of a few other small molecules; the contribution of macromolecules such as proteins, in low concentration in the tears is small [37] in both humans [35] and rabbits [36], the concentrations of Na^+ and HCO_3^- are similar in both tears and plasma [37–39]. In both species, however, the concentrations of K^+ and Cl^- are significantly higher in the tears than plasma, which, in the rabbit [35,40–43] is attributed to the secretion of these ions into the lacrimal fluid by duct epithelial cells. This causes the tears to be hyperosmolar with respect to serum [44] and this possibility cannot be excluded for human lacrimal fluid [35,39,45]. Based on modelling considerations, the contributions of conjunctival and corneal secretions to tear flow in the human has been estimated to be around 10%, but the osmolarity of these fluids is not known [46].

It should be noted that in the human tear literature, in relation to the diagnosis of DED, the term 'tear hyperosmolarity' is used in comparison with the osmolarity of the tears of normal subjects. As noted, this lies in the region of 301–302 mOsm/L. The osmolarity of the conjunctival secretion is not known.

Plasma or serum osmolality (pOsm), measured directly, or estimated from their chemical composition [47,48] has long been used as a clinical index of body hydration [18,49,50] serving as the gold standard against which other less invasive methods are compared in the diagnosis of water-loss dehydration. In normally hydrated subjects, hydration is maintained within narrow limits, [51] which, for plasma, are between 285 and 295 mOsm/kg [18,21,22]. Impending dehydration is defined by a plasma osmolality of > 295 or ≤300 mOsm/kg and clinical or 'current' dehydration is by a plasma osmolality of > 300 mOsm/kg. A problem could arise, in using tOsm measured in open-eye conditions to detect suboptimal body hydration [12]. The prevalence of body dehydration rises with age [14] as does that of DED [52] and hence of tear hyperosmolarity from that cause. Thus, if diagnosis of body dehydration was based on open eye tear samples, the coincident occurrence of tear hyperosmolarity due to a DED mechanism would be a potential source of false positives and lead to increasing misdiagnosis of body dehydration with increasing age.

A means to circumvent this difficulty is proposed here, by measuring tOsm after a period of evaporative suppression. It is hypothesised that a period of eye closure or exposure of the open eyes to an environment of high humidity will drive down tOsm to a basal level that will be individual to a given person and a stable indicator of the body's hydration state. A further prediction is that with continued tear turnover and mixing of the lacrimal, conjunctival and corneal fluids and equilibration of these fluids across the conjunctiva, tOsm will fall to a level close to and determined by, that of the plasma, and therefore subject to its tight control [49]. It will be seen that, if these conditions prevail, then in both normal eyes and DED patients, the tOsm measured immediately after a suitable period of eye closure will lie at a basal level, relatively independent of the nascent level of osmolarity of its constituent fluids and close to that of the plasma. This is termed here, Basal Tear Osmolarity (BTO), and it is proposed that it may serve as an index of body hydration and as a personal baseline against which to gauge the severity of tear hyperosmolarity in an individual case of dry eye.

This background forms the basis of the present study in which tOsm is measured in a group of subjects with healthy eyes and in a group of patients with DED, after a period of either eye closure or exposure to high ambient humidity.

2. Materials and methods

2.1. Ethical approval

Studies were performed according to the Declaration of Helsinki. Ethical approval was obtained from the Research Ethics Committee of Anglia Ruskin University and NRES Committee (South East Coast-Brighton and Sussex). Written consent was obtained from all participants following a verbal and written explanation of the study