Is Whole-Body Hydration an Important Consideration in Dry Eye?

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Purpose. To identify if whole-body hydration plays an important role in dry eye (DE). We hypothesized that individuals classified as DE have higher plasma osmolality (Posm), indicating suboptimal hydration, compared with those classified as non-DE.

Methods. Using a hospital-based observational cross-sectional design, assessment of DE and hydration was performed upon admission in 111 participants ($N = 56$ males and 55 females; mean ± SD age 77 ± 8 years). Assessments of DE included tear osmolarity (Tosm), the 5-item dry eye questionnaire (DEQ-5), rating of eye dryness using a visual analogue scale (VAS), and noninvasive tear film breakup time (NITBUT). Hydration assessment was performed by measuring Posm using freezing-point depression osmometry.

Results. Posm was higher in DE than control (CON), indicating suboptimal hydration when using the 316 mOsm/L Tosm cutoff for DE (mean Posm + 11 mOsm/kg versus CON, $P = 0.004$, Cohen's effect size [d]) = 0.83) and the more conservative Tosm classification for DE where Tosm >324 and CON <308 mOsm/L (mean Posm + 12 mOsm/kg versus CON, $P = 0.006$, $d = 0.94$). Posm was also higher in DE than CON when using composite DE assessments, including Tosm and DEQ-5 ($P = 0.021$, $d = 1.07$); Tosm and NITBUT ($P = 0.013$, $d = 1.08$); and the VAS and DEQ-5 ($P = 0.034$, $d = 0.58$).

Conclusions. These are the first published data to show that individuals classified as DE have higher Posm, indicating suboptimal hydration, compared with non-DE. These findings indicate that whole-body hydration is an important consideration in DE. (*Invest Ophthalmol Vis Sci.* 2012;53:6622–6627) DOI:10.1167/iovs.12-10175

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Dry eye (DE) affects the tears and ocular surface resulting in symptoms of discomfort, visual disturbance, and tear film instability with potential for damage to the ocular surface.[1] Depending upon the population studied, and the clinical assessment methods and definitions adopted,[2] the incidence of DE ranges from 0.1% to as high as 33%.[3] The etiology of DE is, at best, little understood and the current consensus is that DE is of multifactorial origin.[4] There is though widespread agreement that DE is more common in the elderly than the young,[5] and in women than men[5] and also in patients on diuretics,[6] antianxiety drugs,[5] and sex hormone medication.[7,8] A recent study estimated that the overall economic burden on the US healthcare system due to DE is close to $4 billion each year.[9] Interestingly, the losses due to decreased productivity (e.g., due to absenteeism) considerably outweighed the direct costs of care. It goes without saying that DE significantly impacts upon the individual's quality of life[10] and that additional insights to better understand both the etiology of DE, and potential therapeutic treatments for DE are welcome.

The clinical methods often used to identify DE include: questionnaires that assess symptomatology (e.g., the dry-eye questionnaire [DEQ])[11,12] and the ocular surface disease index[13]; tear film breakup time (TBUT) by instilling fluorescein stain[14]; noninvasive TBUT (NITBUT)[15]; conjunctival staining[16]; and the Schirmer test of tear secretion.[14] Tear film osmolarity (Tosm) is currently recognized as a primary biomarker of DE[14,17]; this is largely because raised Tosm is involved in the ocular inflammation in DE[4] and also because measurement of Tosm can now be made using a portable device[18] that avoids the subjectivity inherent in some DE detection methods.

To the best of our knowledge, there are no published studies that have investigated the concept that whole-body dehydration may have a role in DE. We have recently shown progressive increases in Tosm during modest, whole-body dehydration evoked by exercise and overnight fluid restriction; albeit, we used healthy, non-DE adult males and females.[19] Although we evoked only modest dehydration (2%–3% body mass loss), Tosm was greater than the recently proposed 308 mOsm/L threshold for mild/moderate DE[18] in 10 of our 14 moderately dehydrated participants, all of whom had Tosm <308 mOsm/L at the start of the trial (mean Tosm 293 mOsm/L). In addition, providing fluid boluses to improve our participants' whole-body hydration status decreased Tosm. These recent data fuel speculation that whole-body dehydration may play a role in DE[19,20] and that improving whole-body hydration by increasing fluid intake may have a therapeutic effect for DE patients. Considering this, it might not be a coincidence that DE is more common in the elderly than the young[5] as clinical whole-body dehydration (e.g., increase in extracellular tonicity), and its associated impact on morbidity and mortality,[21] is also more prevalent in this population.[22,23] To this end, we recruited an elderly cohort and assessed suitable markers of DE (e.g., Tosm, DEQ, and NITBUT)[11,14,15,17] and whole-body hydration status (plasma osmolality)[23,24] to

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test the hypothesis that those classified as DE have higher plasma osmolality than those classified as non-DE.

Methods

Participants

New admissions to the acute medical unit of Gwynedd Hospital, Bangor, between July and December 2011, were targeted to participate in the study. Those over 60 years of age with capacity to consent were deemed eligible, whilst exclusion criteria for participation included recent eye surgery, contact lens wear within 8 hours, use of eye drops within 2 hours,[14] and known chronic kidney disease. All participants provided fully informed written consent. The study adhered to the Declaration of Helsinki and was approved by the North West Wales Research Ethics Committee. A total of 146 participants met the inclusion/exclusion criteria, with 35 declining to participate. Therefore, data were collected from 111 participants ($N = 56$ males and 55 females; mean age 77 ± 8 years). Of these, tear fluid samples were collected from 99 participants, with seven unable to tolerate the test, and five unable to provide tear fluid.

Experimental Procedures

The study was conducted using a hospital-based observational cross-sectional model. Dry eye assessment and whole-body hydration assessment measures were performed, on admission, within a 30-minute period with no disruption to routine care. Dry eye assessment measures included, in the following order, the 5-item dry eye questionnaire (DEQ-5), rating of eye dryness using a visual analogue scale (VAS), NITBUT, and Tosm. The investigator performing NITBUT and Tosm measurements was not aware of the DEQ-5 or VAS result. Finally, for the whole-body hydration assessment, a blood sample was obtained and analyzed for plasma osmolality (Posm): the kidneys tightly regulate blood osmolality normally between 277 and 281 mOsm/kg.[25] Plasma osmolality is a widely accepted marker of whole-body hydration[24] that has been used to assess static (at one point in time) hydration in the elderly.[23] This approach enabled us to identify if participants classified as DE (see data analysis) have higher Posm than those classified as non-DE (CON). The patient's medical records were accessed to identify those taking medications known to affect tear production (e.g., diuretics, antihistamines, antidepressants, corticosteroids, immunomodulators, and sex hormone medication)[6,14] for further subanalysis.

Dry Eye Assessment

DEQ-5. The DEQ-5 is a validated questionnaire that has been shown to discriminate between different severities of DE.[11] Participants self-assessed the frequency and severity of eye discomfort, eye dryness and watery eyes experienced during the evening[12] of a typical day within the last month. Responses were given using a Likert scale with scoring criteria from 0 = never experienced the symptom to 5 = extremely severe experience of symptom. The sum of the scores from the five questions was used in the analysis.

VAS. Similar to others,[11] participants were asked to place a pencil mark on a 100-mm horizontal line corresponding to their perceived eye dryness in response to the question, "How dry do your eyes feel right now?" The scale was anchored on the left- and right-hand side of the line with the phrases "not at all dry" and "very dry," respectively. The length in mm from the left end of the line to the pencil mark was measured to provide a rating of perceived eye dryness.

NITBUT. Tear film stability was assessed noninvasively using the Tearscope-Plus (Keeler Instruments, Windsor, UK) as previously described.[15,26] The Tearscope-Plus is a handheld device which fits over the eye socket. A light within the device (Keeler Instruments) illuminates the eye and a grid is reflected onto the cornea. Participants were instructed to blink once and then refrain from blinking for as long as possible while the investigator looked for distortion in the reflected pattern. The investigator recorded NITBUT as the elapsed time in seconds between the blink and distortion. This procedure was repeated three times and the median value used in analyses.

Tosm. Tear fluid was collected and analyzed for Tosm using a commercially available device (TearLab Osmolarity System, San Diego, CA) as previously described.[19] Tear fluid was collected from the same eye on which the NITBUT measurement was performed.

Whole-Body Hydration Assessment

Blood samples were collected from an antecubital vein or from the back of the hand into a vacutainer tube containing lithium heparin (Becton Dickinson, Oxford, UK). Blood samples were spun at 1500*g* for 10 minutes at 4°C in a centrifuge. Triplicate measurements of Posm were made using a freezing point depression osmometer (Model 330 MO; Advanced Instruments, Norwood, MA) as described.[19] The analytical coefficient of variation for repeated Posm measurements was 0.7% (2 mOsm/kg).

Data Analysis

To identify participants with DE, we have used three different approaches for group comparisons. The first approach classified DE using Tosm alone. Here we used the recently proposed single Tosm cutoff value of 316 mOsm/L,[27] whereby participants with a Tosm >316 mOsm/L formed the DE group and those with a Tosm ≤316 mOsm/L formed the CON group. We also used a Tosm grouping based upon the modified DEWS Severity Scale,[14] whereby those with a Tosm >324 mOsm/L formed the DE group, and those with a Tosm <308 mOsm/L formed the CON group. For the second, more conservative approach to DE classification, we adopted composite measures of DE as recently recommended.[14] Participants had to fulfill two criteria to be classified as DE, which included a Tosm >324 mOsm/L and a DEQ-5 score ≥6, as previously described.[11] In this classification, CON were those with Tosm <308 mOsm/L and DEQ-5 <6. Also, participants were classified based upon a composite of Tosm >324 mOsm/L and a NITBUT <10 seconds, as previously described.[15,26] In this classification, CON were those with Tosm <308 mOsm/L and NITBUT ≥10 seconds. The data for each of the classifications described above are presented two ways; first, excluding those participants taking medications known to cause eye dryness (e.g., diuretics, antihistamines, antidepressants, corticosteroids, immunomodulators, and sex hormone medications)[6,14]; and second, by presenting the data for all participants, regardless of medication. The group means ± SD for each ocular measurement for each of the above approaches to classify DE and CON are presented in Table 1. The third and final approach we have adopted to classify groups used only self-reported subjective measures of DE, where those participants who demonstrated both a VAS ≥6 (mean ± SD, 7.5 ± 1.0) and a DEQ-5 ≥6 (mean ± SD 9.7 ± 3.5) formed the DE group, while those with a VAS <6 (mean ± SD, 1.2 ± 1.5) and a DEQ-5 <6 (mean ± SD, 1.9 ± 1.8), formed the CON group. A sample size calculation was performed to determine the minimum N to identify a significant difference in Posm between DE and CON. An $N = 11$ in each group was required to detect a meaningful difference in Posm of 9 mOsm/kg,[24] using a population standard deviation from an elderly cohort,[28] with α and β set at 0.05 and 0.8, respectively. All between group differences (CON and DE) were analyzed using independent *t*-tests. In addition, the meaningfulness of group differences was also calculated using a Cohen's d effect size using the following equation:

$$\text{Cohen's } d = (\bar{X}_1 - \bar{X}_2)/\text{Pooled SD}$$

where $\bar{X}_1$ is the mean of DE, and $\bar{X}_2$ is the mean of CON. Cohen's d effect sizes greater than 0.2, 0.5, and 0.8 represent small, medium, and large effects, respectively.[29] Finally, a Pearson's correlation was performed to determine the association between Posm and Tosm. All data were analyzed using statistical software (SPSS version 14;

Table 1. Ocular Characteristics for DE and CON Groupings

	Tosm, DE >316†	Tosm, DE >324‡	Tosm and DEQ-5§		Tosm and NITBUT‖	
	Tosm, mOsm/L	Tosm, mOsm/L	Tosm, mOsm/L	DEQ-5	Tosm, mOsm/L	NITBUT, s
No medications						
DE	346 ± 28*	354 ± 27*	356 ± 30*	10.1 ± 3.9*	361 ± 31*	6.2 ± 2.0*
CON	297 ± 14	291 ± 12	286 ± 11	2.0 ± 2.4	292 ± 13	15.8 ± 5.3
All participants						
DE	347 ± 28*	356 ± 27*	356 ± 28*	8.9 ± 3.2*	357 ± 27*	6.8 ± 2.2*
CON	300 ± 13	293 ± 11	290 ± 10	2.1 ± 2.0	294 ± 11	21.1 ± 10.9

Data are presented with participants excluded who were taking medications known to cause eye dryness (no medications row), and for all participants. Data are shown for DE and CON classifications.

* $P < 0.01$ DE significantly different than CON.

† Tear osmolarity (Tosm) alone using a single cut-off of 316 mOsm/L.

‡ Tosm alone using two cutoffs, DE >324 mOsm/L, CON <308 mOsm/L.

§ A composite of Tosm and DEQ-5 responses where DE Tosm >324 mOsm/L and DEQ-5 ≥6 and CON Tosm <308 mOsm/L and DEQ-5 <6.

‖ A composite of Tosm and NITBUT where DE Tosm >324 mOsm/L and NITBUT <10 seconds and CON where Tosm <308 mOsm/L and NITBUT ≥10 seconds.

MathWorks, Natick, MA). Data in the text and figures are presented as mean ± SD. Statistical significance was accepted at $P < 0.05$.

Results

DE Classified Using Tosm

In participants who were not taking any medication known to cause eye dryness, those classified as DE using Tosm alone presented with a significantly higher Posm than CON using both the single Tosm 316 mOsm/L cutoff (mean Posm + 11 mOsm/kg versus CON, $P = 0.004$, Cohen's $d = 0.83$, Fig. 1A) and the more conservative classification where DE Tosm >324 and CON <308 mOsm/L (mean Posm + 12 mOsm/kg versus CON, $P = 0.006$, Cohen's $d = 0.94$; Fig. 1B). This finding was highly significant and gave large effect sizes. There were also significant differences and small-medium effect sizes when all participants, including those taking medications known to cause eye dryness, were included. For example, Posm was higher in DE than CON when using the single Tosm 316 mOsm/L cutoff ($P = 0.039$, Cohen's $d = 0.36$; Table 2) and the more conservative Tosm classification where DE Tosm >324 and CON <308 mOsm/L ($P = 0.045$, Cohen's $d = 0.42$; Table 2). There was a small but significant correlation between Tosm and Posm ($r = 0.34$, $r^2 = 0.12$, $P = 0.021$). The mean Posm for the five participants for whom tear fluid samples could not be collected after three attempts (even though they could all tolerate the procedure) was 292 ± 5 mOsm/kg.

DE Classified Using Composite Assessments

Using composite measures to classify DE—and with medications known to cause eye dryness excluded—once again, participants classified as DE exhibited significantly higher Posm than CON which, despite the small sample size, resulted in very large effect sizes (Figs. 2A, 2B). For example, Posm was higher in DE than CON when using Tosm and DEQ-5 to classify DE (mean Posm + 14 mOsm/kg versus CON, $P = 0.021$, Cohen's $d = 1.07$; Fig. 2A) and when using Tosm and NITBUT to classify DE (mean Posm + 13 mOsm/kg versus CON, $P = 0.013$, Cohen's $d = 1.08$; Fig. 2B). When all participants were considered, including those taking medications known to cause eye dryness, there was a significant effect upon hydration when groups were stratified using Tosm and DEQ-5 ($P = 0.024$, Cohen's $d = 0.70$; Table 2). There was a trend for a higher Posm in DE than CON when groups were stratified using Tosm and NITBUT ($P = 0.089$, Cohen's $d = 0.44$; Table 2).

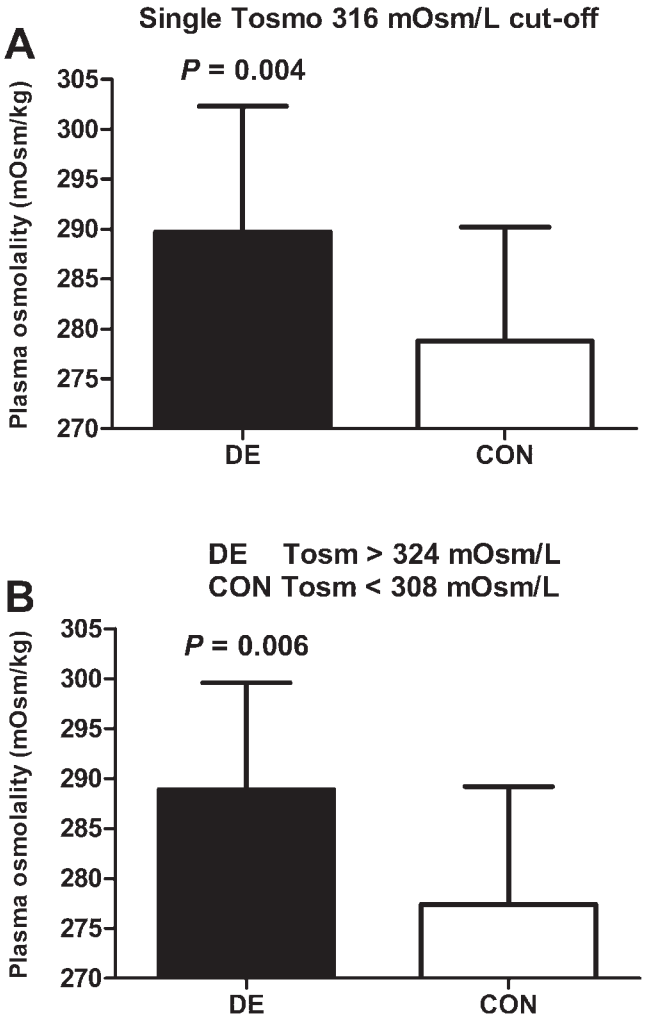

Figure 1. Whole-body hydration status assessed using plasma osmolality in participants classified as DE using Tosm after removal of participants on known ocular drying medications. Data for plasma osmolality shown in *panel A* use a single Tosm cutoff of 316 mOsm/L (DE >316, CON ≤316 mOsm/L), and *panel B* where DE Tosm >324 mOsm/L and CON <308 mOsm/L. Data are mean ± SD. Cohen's *d* effect sizes were 0.83 and 0.94 for (**A**) and (**B**) indicating "large" effects. *Panel A*: DE $N = 26$ and CON $N = 15$. *Panel B*: DE $N = 20$ and CON $N = 10$.

Table 2. Whole-Body Hydration Status Measured by Posm in All Participants (Including Those Taking Medication) for DE and Non-DE CON Groups

	Tosm Alone, 316 Cutoff†	Tosm Alone, >324 and <308 Cutoff‡	Tosm and DEQ-5§	Tosm and NITBUT‖
Plasma osmolality, mOsm/kg				
DE (*N*)	288 ± 11* (54)	288 ± 10* (31)	288 ± 12* (17)	287 ± 10 (22)
CON (*N*)	284 ± 10 (45)	284 ± 11 (28)	279 ± 13 (14)	283 ± 10 (17)
Cohen's *d*	0.36	0.42	0.70	0.44

$N = 99$, Data shown are for DE and CON classifications.
* $P < 0.05$ DE significantly higher than CON.
† Tear osmolarity (Tosm) alone using a single cut-off of 316 mOsm/L.
‡ Tosm alone using two cutoffs, DE >324 mOsm/L, CON <308 mOsm/L.
§ A composite of Tosm and DEQ-5 responses where DE Tosm >324 mOsm/L and DEQ-5 ≥6 and CON Tosm <308 mOsm/L and DEQ-5 <6.
‖ A composite of Tosm and NITBUT where DE Tosm >324 mOsm/L and NITBUT <10 seconds and CON where Tosm <308 mOsm/L and NITBUT ≥10 seconds.

DE Classified Using Self-Report Assessments

Using this approach, Posm in DE was significantly higher than CON (mean Posm + 6 mOsm/kg versus CON, $P = 0.034$; Fig. 3), where Cohen's $d = 0.58$ indicated a medium effect.

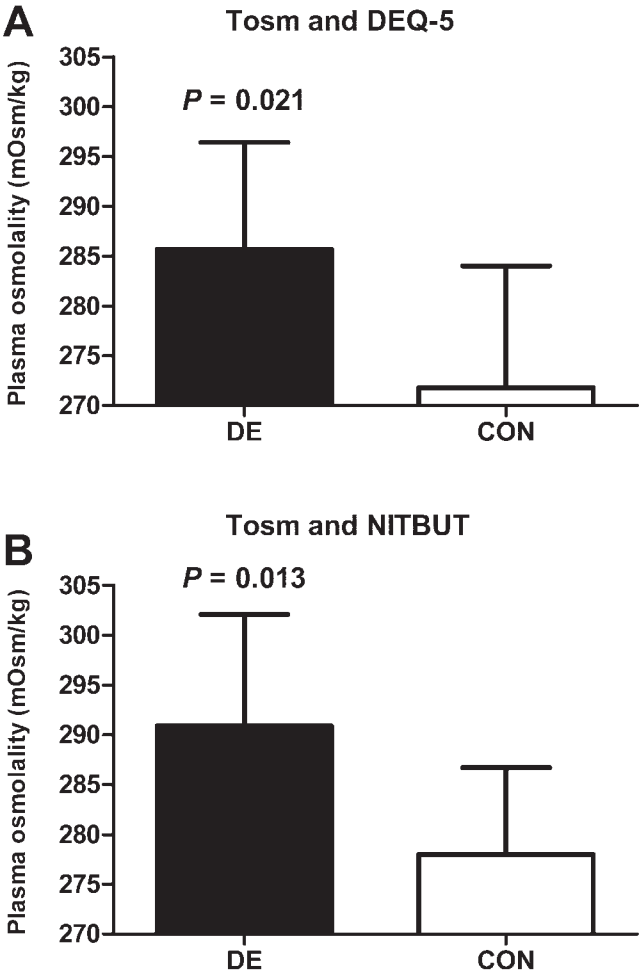

Figure 2. Whole-body hydration status assessed using plasma osmolality in participants classified as DE using composite DE assessments after removal of participants on known ocular drying medications. Data for plasma osmolality are shown in *panel A* where DE Tosm >324 mOsm/L and DEQ-5 ≥6 and CON Tosm <308 mOsm/L and DEQ-5 <6. Data shown in *panel B* where DE Tosm >324 mOsm/L and NITBUT <10 seconds and CON where Tosm <308 mOsm/L and NITBUT ≥10 seconds. Data are mean ± SD. Cohen's *d* effect sizes were 1.07 and 1.08 for (**A**) and (**B**) indicating "large" effects. *Panel A*: DE $N = 8$ and CON $N = 6$. *Panel B*: DE $N = 12$ and CON $N = 6$.

Discussion

The aim of the present study was to identify whether whole-body hydration status is an important consideration in DE. To achieve this aim, we recruited an elderly cohort in an observational, cross-sectional design and assessed suitable markers of DE (e.g., Tosm, DEQ, and NITBUT)[11,14,15,17] and whole-body hydration status (Posm).[23,24] The data support our hypothesis and, to the best of our knowledge, are the first to show that participants classified as DE have higher Posm, indicating suboptimal whole body hydration, than those classified as non-DE. This effect was apparent using a number of different methods to classify DE. Future studies should identify whether improving whole body hydration in a rigorous fluid intervention experimental model confers important therapeutic effects for patients with DE. Besides the widely accepted advantages of maintaining euhydration for optimal cognitive function, physical function and health,[21–23] the current findings indicate that whole-body hydration status is also an important consideration in DE, at least in the elderly.

The current findings support our hypothesis, and our recent speculation,[19,20] that whole-body hydration may play a role in DE. Recently, in healthy young adults, we showed a progressive increase in Tosm during modest, whole-body dehydration and a decrease in Tosm after fluid boluses to improve our participants' whole-body hydration.[19] Although the mechanism(s) by which whole body hydration influences Tosm remains to be elucidated, we hypothesize that tear secretion decreases with progressive dehydration, thus concentrating the tear fluid (i.e., increasing Tosm) in a manner similar to which the decrease in saliva flow rate with

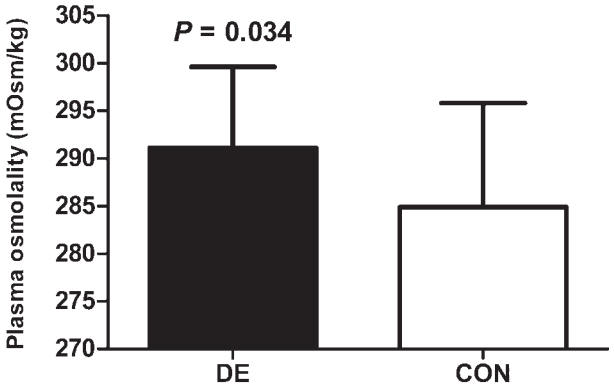

Figure 3. Whole-body hydration status assessed using plasma osmolality in all participants classified as DE where the VAS reading for eye dryness was ≥6 cm and DEQ-5 was ≥6 ($N = 12$) and CON where VAS <6 cm and DEQ-5 <6 ($N = 57$). Data are mean ± SD. Cohen's *d* effect size = 0.58 indicates a "medium" effect.

progressive whole body dehydration is known to increase saliva osmolality.[30,31] This hypothesis requires investigation in appropriately designed whole-body dehydration studies that make parallel measures of tear secretion and Tosm. Given that raised Tosm is involved in the ocular inflammation in DE,[4] any variable that influences Tosm must be given due consideration in the context of both the etiology of DE and the treatment of the various types of DE. Future studies should identify whether whole-body hydration is an important consideration in the various types and subcategories of DE as described in the DEWS report (e.g., aqueous-deficient DE and evaporative DE), as we recognize that we didn't make such distinctions in the present study.[1] Although we did not assess inter-eye Tosm variability, as has recently been suggested to be a hallmark of DE,[18] we have shown a significant and meaningful difference in whole-body hydration status between participants categorized as DE and CON using a stringent Tosm stratification (whereby DE Tosm >324 mOsm/L using the modified DEWS Severity Scale; Fig. 1B).[14] Also, when using a range of composite DE clinical assessment tools as recently recommended (Figs. 2A, 2B)[14] and when using our total participant cohort in comparisons, the significant difference in whole body hydration between DE and CON was still evident when including participants on medications known to cause eye dryness (Table 2).

Whole-body hydration status has been assessed with varying degrees of success using urine,[32,33] saliva,[30,31] and tears,[19] but Posm is the most widely accepted whole-body hydration marker.[24] Studies investigating whole-body hydration in the elderly often adopt a Posm dehydration threshold of 295 mOsm/kg[23,34]; but due to the ease and availability of automated analyzers, Posm is often "calculated" rather than "directly measured." The direct measurement of Posm using freezing point depression is the preferred method.[35] The calculation of Posm has also been performed various ways, further adding to the confusion—for example, using Equation (*1*): $(2 \times [\text{sodium} + \text{potassium}]) + (\text{glucose})$[23] or Equation (*2*): $(2 \times [\text{sodium} + \text{potassium}]) + (\text{glucose}) + (\text{blood urea nitrogen})$,[34] where units are mmol/L. Calculating Posm typically results in higher readings than directly measuring Posm.[36] In a separate study in our laboratory, we collected 94 blood samples and measured Posm using freezing point depression and calculated Posm using Equations (*1*) and (*2*). We found that calculating Posm resulted in a mean bias of +3 mOsm/kg for Equation (*1*) and +12 mOsm/kg for Equation (*2*) (Fortes MB, unpublished observation, 2011). Taking this positive bias for calculated Posm into account, the measured Posm in our participants classified as DE (Figs. 1–3, and Table 2) are equivalent to, or exceed, the 295 mOsm/kg dehydration threshold adopted in studies of whole-body hydration in the elderly using calculated Posm.[23,34] In addition, it is important to reiterate our finding that the difference in measured Posm between participants classified as DE and CON (e.g., DE Posm +14 mOsm/kg versus CON, Fig. 2A) is meaningful[24] and represents suboptimal whole-body hydration in DE.

The present findings showing suboptimal whole-body hydration in DE versus non-DE individuals raise the exciting prospect that improving whole-body hydration with fluid intervention might confer important therapeutic effects for patients with DE. Indeed, under tightly controlled laboratory conditions, we have recently shown—albeit in non-DE individuals—that fluid boluses decrease Tosm to baseline levels after Tosm was raised by whole-body dehydration.[19] Also, reducing the osmolarity of the tear film using hypotonic eye drops (150 mOsm/L) rather than isotonic eye drops (300 mOsm/L) has been shown to decrease DE symptoms in DE patients:[37] this lends further support to the premise that raised Tosm is central in DE[4] and the concept that decreasing Tosm through improvements in whole body hydration might also decrease DE symptoms. To examine this further, we performed a small pilot study where we collected plasma and tear fluid samples in an elderly mild/moderate DE[18] cohort ($N = 8$) whose initial Tosm was >308 mOsm/L and who showed an improvement in whole-body hydration (decrease in Posm) during a 48-hour hospital stay. The improvement in whole-body hydration in these modestly dehydrated patients (decrease in Posm from 296 ± 14 to 289 ± 13 mOsm/kg) was accompanied by a significant decrease in Tosm from 335 ± 33 to 308 ± 10 mOsm/L ($P = 0.038$, Cohen's $d = 0.96$ indicating a large effect; Fortes MB, unpublished observations, 2011). After excluding patients on ocular drying medications, the remaining five patients still showed a large effect for the reduction in Tosm from 336 ± 36 to 312 ± 10 mOsm/L with improved whole-body hydration (Cohen's $d = 0.86$), albeit this did not reach statistical significance ($P = 0.112$). Clearly, large-scale studies are needed to confirm that improving whole-body hydration status in a rigorous fluid intervention experimental model confers important therapeutic effects for patients with DE.

In conclusion, these are the first published data to show that individuals classified as DE using a number of different methods have higher Posm, indicating suboptimal whole-body hydration, compared with those classified as non-DE. Large-scale studies are required in DE patients to identify whether improving whole-body hydration may serve as a therapy to reduce DE symptoms.

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