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Full Length Article

Processed egg yolk supplementation for the treatment of dry eye disease and meibomian gland dysfunction – pilot study

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Background

Current treatment modalities in the management of dry eye disease (DED) reflect its multifactorial pathophysiology. While dietary modifications have been advocated in the treatment of DED and meibomian gland dysfunction (MGD), the clinical benefits of processed egg yolk (PEY) supplementation in DED are unknown. Our aim was to analyze the benefits of oral PEY supplementation in DED and MGD.

Methods

Prospective, two-center, noncomparative, interventional study. Patients with mild-to-moderate DED and MGD, on artificial tear drop treatment alone, and refractory to treatment underwent a 6-week period of oral supplementation with 500 mg PEY capsules (WEYE®). Pretreatment data included demographic data, systemic and previous ocular treatments, ocular surface disease index (OSDI) score, tear break-up time (TBUT), basal tear secretion, and modified Oxford ocular surface staining grade. Outcomes analyzed after supplementation with PEY capsules were changes in OSDI, TBUT, basal tear secretion, and ocular surface staining grade compared with baseline.

Results

Twenty-five patients were included. After 6-week supplementation with PEY capsules, statistically significant improvements were observed in median OSDI score (p=0.001) and in mean TBUT (p=0.004), but not in in mean basal tear secretion (p=0.108). Improvement in ocular surface staining grading was observed in 8 (32%) eyes. Worsening of OSDI scores and ocular staining grade were noted in 3 (12%) and 2 (8%) of patients, respectively.

Conclusions

In our study, oral PEY supplementation significantly improved signs and symptoms in patients with mild-to-moderate DED and MGD. Our findings support the utility of dietary modifications the management of DED and MGD, improving ocular surface health and reducing the disease impact and treatment burden.

INTRODUCTION

The awareness of dry eye disease (DED) has risen considerably worldwide in recent years, with significant progress in the understanding of the risk factors, etiology and pathophysiology of the disease (Craig et al. 2017; Stapleton et al. 2017) The high prevalence of DED, the significant impact in the quality of life of patients, and the complex management of DED render this disease a challenge for ophthalmologists.

The multiplicity of therapeutic strategies in DED largely reflects the multifactorial nature of the disease and the need for individualized approaches for each patient. The Tear Film and Ocular Surface Society's Dry Eye Workshop II group (TFOS DEWS II) has grouped treatment strategies for the management of DED in eight large categories: 1) treatments for tear insufficiency, including tear replacement approaches, tear conservation approaches, and tear stimulation approaches; 2) treatments for lid abnormalities, including management of anterior blepharitis and strategies for the treatment of meibomian gland dysfunction (MGD); 3) anti-inflammatory therapy; 4) surgical approaches; 5) dietary modifications; 6) environmental modifications, including modifications in topical and systemic drugs, and modifications in the external environment and in digital device usage; 7) complementary therapies; and 8) management of psychological factors and physical activity (Jones et al. 2017). Although the mainstay of therapy involves artificial tear drops to supplement the tear film, this treatment modality only compensates the aqueous-deficient component of DED, provides only temporary symptomatic relief, and patient compliance and persistence with

long term treatment are low (Swanson 1998; Alghamdi et al. 2017). Besides, even in patients with good adherence to tear drop therapy up to two-thirds of patients remain symptomatic (Downie et al. 2019).

Dry eye is characterized by a loss of the tear film homeostasis, and the mechanisms implicated in the pathophysiology of DED include tear film instability, hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities. In addition, meibomian gland dysfunction (MGD), defined as a chronic, diffuse abnormality of the meibomian glands, is highly prevalent in the elderly population (Alghamdi et al. 2016; Hassanzadeh et al. 2020) and is the leading cause of DED symptoms due to increased water evaporation from the optical surface and disruption of the ocular surface health (Chhadva, Goldhardt, and Galor 2017; Daniel Nelson et al. 2011; Al-Namaeh 2020) The relationship between complex interplay between dietary nutrients and ocular surface health has risen the interest in the field of nutrient supplements as an approach in the treatment of DED and MGD. Oral antioxidants, such as vitamin A or multivitamins have shown to improve tear film stability and the health of the ocular surface (Huang, Yeh, and Hou 2016). Omega-3 (ω-3) essential fatty acids (EFAs) must be ingested from dietary sources (hence the name "essential"), are components of the cell membranes, and its derivatives are implicated in a number of physiologic roles in the ocular surface, including the modulation of inflammation and improving the quality of the meibomian gland secretions, in addition to displaying epitheliotrophic and neuroprotective abilities (Deinema et al. 2017).

Processed egg yolk (PEY) is a regenerative organic matrix composed of over 800 molecules, including neurotrophic lipids, proteins, growth factors, vitamins, and nucleotides. PEY is a bulk of molecules extracted from fertilized and heat-treated egg yolk, which has demonstrated anti-inflammatory, regenerative, and neuroprotective properties in a number of human tissues (Cunill et al. 2017). Clinical evidence of the benefits of PEY supplementation has been demonstrated in rehabilitation and sports medicine (unpublished data), improving the physiologic response to moderate intensity and duration exercise (improved control of cardiac frequency, reduced inflammatory response), improving the sensation of fatigue, and reducing chondral and joint pain owing to its ability to accelerate the regenerative process (unpublished data). In addition, clinical studies are underway in the field of Dermatology, since pre-clinical studies have provided evidence for PEY's skin regenerative and anti-inflammatory effects in skin cells. Pre-clinical studies have found PEY has neuroprotective and neuroregenerative abilities, suggesting potential applications in neurologic diseases such as multiple sclerosis (Cunill et al. 2017).

The aim of this study was to determine the efficacy of a novel PEY-based oral supplement in the management of patients with DED refractory to lubricants.

MATERIALS AND METHODS

This was a prospective, interventional, non-comparative, two-center study. We included subjects over 18 years of age in the study if they had a previously confirmed diagnosis of DED and MGD, with a minimum follow-up of 6 months for symptomatic DED at the study centers, who were exclusively on artificial tear drop substitutes (frequency of treatment from 5 to 12 daily instillations (sodium hyaluronate 0.15% eye preservative-free drops (Hyabak, Théa Laboratoires, Clermont-Ferrand, France) or an association of trehalose 3% and sodium hyaluronate 0.15% preservative-free eye drops (Thealoz Duo, Théa Laboratoires, Clermont-Ferrand, France) plus nighttime gel or ointments – either sodium hyaluronate 0.15% and xanthan gum 1%, (Lubristil Gel, Angelini Pharma, Roma, Italy) or vitamin A palmitate and paraffin (Aquoral Noche, Esteve Pharmaceuticals, Barcelona, Spain)) and were refractory to this artificial tear drop regime for at least 3 months.

Inclusion criteria included an Ocular Surface Disease Index (OSDI) score between 13-32, a Schirmer test under anesthesia > 2 mm/5 min and ⩽ 10 mm/5 min, and an ocular surface (with fluorescein dye) staining grade < 3, according to the modified Oxford ocular surface staining scale. Exclusion criteria included contact lens wearers, eyelid position abnormalities, use of topical anti-inflammatory medications within 3 months of recruitment, recent changes in systemic medications (< 3 months before recruitment and during the study period), any ocular surgery within 3 months of recruitment, pregnancy, poor compliance to topical tear drop treatment, and inability to understand the treatment and the study. This study was conducted in compliance with the tenets of the Declaration of Helsinki.

Subjects underwent supplementation with oral 500 mg PEY capsules (WEYE® Wellness SL, Barcelona, Spain) for a 6-week period, in a regiment consisting of 6 capsules daily for 2 weeks, followed by 3 capsules daily for the remaining 4 weeks; subjects were also instructed to remain on artificial tear drop treatment. WEYE® is a PEY-based nutraceutical, containing 800 bioactive molecules, including growth factors, neurotrophic and immunomodulatory lipids, vitamins, enzymes and hormones, expressed at much larger concentrations compared with the commercial eggs (Cunill et al. 2017).

Baseline data collected included patient age, gender OSDI score, ocular surface staining grade with modified Oxford ocular surface staining scale, tear break-up time (TBUT, seconds) measured clinically, and basal tear secretion with Schirmer's test under anesthesia (mm/5min). Outcomes analyzed at 6 weeks after initiation of WEYE® included changes in OSDI score, TBUT, ocular surface staining grade of the eye with the most severe grade before treatment with PEY, and basal tear secretion.

Statistical analysis was performed using SPSS software (v 23.0; IBM Corp, Chicago, Illinois, USA). Quantitative variables were described as mean (standard deviation) or as median (P75-P25) depending on whether they had a normal distribution. Parametric or nonparametric tests were applied depending on whether variables had a normal distribution. Categorical variables were described as absolute and relative frequencies. Chi-square or Fisher exact tests were applied for comparison between categorical variables. The level of significance α for the statistical analysis was 0.05.

Table 1. Patient characteristics and dry eye disease parameters at baseline (n = 25).

Age (years)	69.1 ± 7.5
Gender (female n, %)	21 (84%)
Previous treatments for DED	Artificial tear drops – 25 (100%) / Punctal plugs – 3 (12%)
Relevant PMH	T2DM – 3 (12%) / Antidepressants – 4 (16%)
OSDI score	20 (IQR 16-25)
TBUT (seconds)	6.08 ± 0.60
Oxford corneal staining grade (0-2)	7 (28%) Grade 0 / 7 (28%) Grade 1 / 11 (44%) Grade 2
Basal tear secretion (mm/5min)	5.88 ± 0.41

Legend: Values are reported as mean (SD) or as median (P25-P75) depending on whether variables followed a normal distribution. Categorical variables are presented as absolute and relative frequencies.
DED – dry eye disease; PMH – past medical history; T2DM – type 2 diabetes mellitus; OSDI – ocular surface disease index; TBUT – tear break-up time.

RESULTS

Twenty-five eyes of 25 patients (84% female patients) with mild-to-moderate DED and MGD were included in this study. Baseline data are presented in Table 1. Mean patient age was 69.1 ± 7.5 years. Three patients (12%) had previously undergone treatment with temporary punctal plugs, while all the remaining study subjects had only been treated with artificial tear drops. Relevant systemic medication history was positive for antidepressants in four subjects (16%) and oral hypoglycemic drugs for type 2 diabetes mellitus (T2DM) in three subjects (12%). Baseline ocular surface Oxford staining grades were Grade 0 in seven eyes (28%), Grade 1 in seven eyes (28%), and Grade 2 in eleven eyes (44%).

Outcomes of treatment are presented in Figures 1 to 4. There was a statistically significant decrease in median OSDI score from 20.0 (IQR = 16-25) at baseline to 15.0 (IQR = 10-19) after 6 weeks of treatment with PEY (p-value = 0.001) (Figure 1).

Mean TBUT improved from 6.08 ± 0.60 seconds at baseline to 7.80 ± 0.62 seconds after 6 weeks of supplementation with PEY (Figure 2); this change was statistically significant (mean change in TBUT from baseline = 1.72 ± 2.67 seconds; 95% CI 0.62-2.82 seconds; p-value = 0.004).

Mean baseline basal tear secretion was 5.88 ± 0.41 mm/5 min. At 6 weeks of supplementation with PEY, mean basal tear secretion improved to 6.56 ± 0.47 mm/5min (Figure 3); however, this difference did not reach statistical significance (mean difference = 0.68 ± 2.04 mm/5min; p = 0.108).

The ocular fluorescein staining grading improved in 8 of 25 eyes (32.0%) after 6 weeks of supplementation with PEY, with 2 out of 7 eyes healing to grade 0 ocular surface staining from grade 1 at baseline (28.6%), and with 6 out of 11 patients (54.5%) improving from Grade 2 to Grade 1 ocular surface staining (Figure 4). Three patients (12%) worsened the OSDI score by 2-3 points, one of which had worsened ocular surface staining grade by one step; this was an elderly woman on antidepressant medication. Increased ocular surface staining grade was observed in two cases (8%); the second patient with increased staining grade was a diabetic, postmenopausal patient, in which the OSDI symptom score decreased by 17 points after supplementation with WEYE® but ocular surface health worsened in fluorescein dye testing.

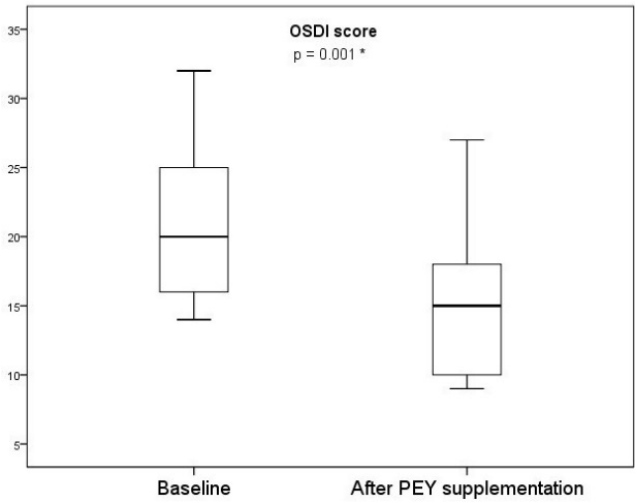

Figure 1. Box-plot diagrams of ocular surface disease index scores (OSDI) at baseline (left) and after 45 days of supplementation with processed egg yolk (PEY) capsules. A statistically significant improvement in median OSDI was observed after treatment with PEY supplementation compared with baseline (Wilcoxon's signed rank test p-value = 0.001).

DISCUSSION

There has been an increasing interest in the dietary modifications for the management of DED. In our study, PEY improved the tear film stability, improving the ocular surface epithelial status, and the symptoms of DED. It is likely that the clinical benefits of PEY supplementation in the treatment of DED is multifactorial, leading to improvement in ocular surface health and homeostasis. PEY has been shown to optimize the immune response, by downregulating proinflammatory molecules, by upregulating suppres-

sive molecules, and possibly by improving the resilience of immune functions to respond to external stressors (Cunill et al. 2020). Oral antioxidants, such as vitamin A, multivitamins and combined formulations of antioxidants and EFAs have shown to decrease the levels of proinflammatory mediators in the ocular surface and to improve tear film stability and the health of the ocular surface (Huang, Yeh, and Hou 2016; Pinazo-Durán et al. 2013; Drouault-Holowacz et al. 2009; Gatell-Tortajada 2016)

In addition, PEY is rich in growth factors, including insulin-like growth factor 1 (IGF-1), neurotrophic growth factor (NGF), lipids, hormones, oligoelements, and enzymes, and has neurotrophic and tissue regenerative abilities (Cunill et al. 2017). Tear levels of IGF-1 have been found to be higher in young adults and to significantly decrease with ageing, that lower levels of IGF-1 are associated with clinical signs of dry eye (Patel, Zhu, and Robertson 2018), and that IGF-1 acts on human meibomian gland epithelial cells to stimulate Meibomian gland function (Ding and Sullivan 2014). Increasing clinical evidence has shown that NGF is an essential neurotrophic and epitheliotropic factor in the cornea and conjunctiva, increasing tear production and increasing conjunctival goblet cell density and function (mucin production and release), and topical recombinant human NGF eye drops have shown to significantly improve signs and symptoms in patients with DED (Sacchetti et al. 2020). In addition, WEYE capsules also contain vitamins A, C, D3 and E. Vitamin A has multiple functions in the eye, being essential in the visual phototransduction cycle, and also playing a major role in the ocular surface homeostasis, including epithelial cell growth and differentiation, conjunctival goblet cell health, and immunological system maintenance (Sommer 1983). Vitamin D plays important roles in ocular surface homeostasis, with increasing clinical evidence supporting the benefits of vitamin D supplementation in the management of DED in patients with vitamin D deficiency (Yang et al. 2018; Liu, Dong, and Wang 2020; Bae et al. 2016), as well as recent evidence of the potential benefits of topical vitamin D in a recent randomized clinical trial (Fogagnolo et al. 2020). Vitamins C and E have antioxidant properties, and vitamin supplementation has shown to improve tear film stability, tear secretion, goblet cell densities, and ocular surface health in diabetic patients (Peponis et al. 2002).

It has been increasingly hypothesized that the ocular surface tissues are very sensitive to dietary changes, and it has been suggested that ω-3 and ω-6 EFAs have beneficial effects in meibomian gland secretion, in lowering ocular surface inflammation, and in increasing tear production (Gatell-Tortajada 2016; Epitropoulos et al. 2016; Molina-Leyva et al. 2020). In the PREDIMED-PLUS trial (a multicenter, randomized, primary prevention study of cardiovascular disease in patients with metabolic syndrome) patients with DED improved ocular signs (OSDI score, TBUT, Schirmer's test, and Oxford staining grade) with Mediterranean diet, particularly patients undergoing a more intensive regime which consisted of Mediterranean diet plus additional calorie restriction and increased physical activity. A recent systematic review found that ω-3 supplementation is beneficial in patients with MGD, improving tear film stability and TBUT (Al-Namaeh 2020). However, the findings

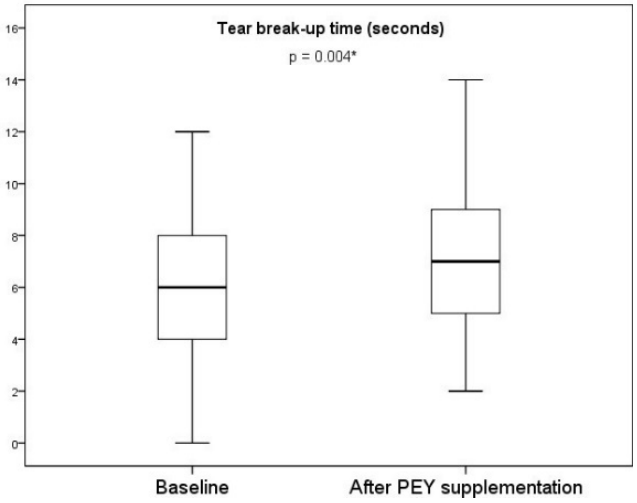

Figure 2. Box-plot diagrams of tear break-up time (TBUT, seconds) at baseline (left) and after 45 days of supplementation with processed egg yolk (PEY) capsules. A statistically significant improvement in mean TBUT was observed after treatment with PEY supplementation compared with baseline (p-value = 0.004).

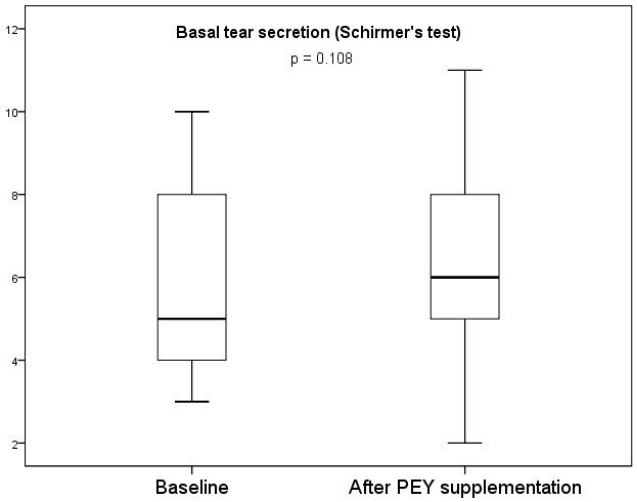

Figure 3. Box-plot diagram of basal tear secretion using Schirmer's test under topical anesthesia before (left) and after 45 days of supplementation with processed egg yolk (PEY) capsules. The increase in mean basal tear secretion after treatment with PEY compared with baseline was not statistically significant (p-value = 0.108).

of a Cochrane systematic review suggested that, while the level of evidence for improvement in OSDI score was moderate, overall the benefit of ω-3 EFA supplementation in the treatment of DED is uncertain and inconsistent (Downie et al. 2019).

Our study has some limitations, including a relatively short follow-up period, a small sample size, and lack of a control group. However, this was a pilot study assessing the efficacy of PEY intake, and we believe that the subjects may be considered their own controls, as inclusion in this study required that patients were refractory artificial tear drop treatment alone. We consider that future studies could opt for a crossover, placebo study design to ascertain the benefits of PEY supplementation (as well as for other dietary supplements under investigation for the treatment of DED). In addition, we cannot exclude that subject compliance and adherence to topical therapy (artificial tears) improved, as study subjects may tend to increase treatment compliance (Swanson 1998). While most patients reported reduced requirement for instillation of artificial tear substitutes, we did not measure specifically the changes in frequency of tear drop treatment. No patients were off tear substitutes since we consider nutraceuticals ought to be considered as a complementary treatment with tear substitutes for patients with DED and MGD. Likewise, we cannot exclude that external, environmental factors may have improved as well, including other dietary modifications and environment changes (for example, less dry environments or reduced digital device usage), although we find this unlikely, as this was assessed at the last follow-up interview with the study subjects. Perhaps future studies of dietary supplementation and nutraceuticals for DED could incorporate a diary log in which study subjects would register meals daily and exercise time per day, as well as an approximate description of indoor time and time of exposure to air conditioner. Another important limitation is that the biodisponiblity of growth factors and other molecules following oral intake of PEY has not yet been studied. This is the main reason why we cannot identify and isolate any of the main components of this regenerative matrix that contribute to the clinical improvement observed in this study. Finally, we did not analyze the levels of growth factors nor analytical biomarkers of ocular surface homeostasis and inflammation in the tear film, which would have strengthened the relevance of our clinical findings.

In conclusion, oral intake of PEY showed a significant clinical improvement in tear film stability, ocular surface health, and symptoms in patients with mild-to-moderate DED. Of note, dietary modifications and nutrient supplementation do not replace for treatment with lubricating artificial tear drops. However, the use of these novel approaches may improve the vision-related quality of life in patients with DED without the associated burden of more aggressive, multimodal forms of treatment, including anti-inflammatory medication. Since DED and MGD are chronic conditions requiring lifetime management, it is likely that prolonged PEY supplementation would be beneficial, and subsequent studies are encouraged to determine the minimum doses required to maintain the clinical benefits observed in the present study. Larger studies with longer follow-up times are encouraged to ascertain the clinical benefits of PEY-based supplements in the management of DED.

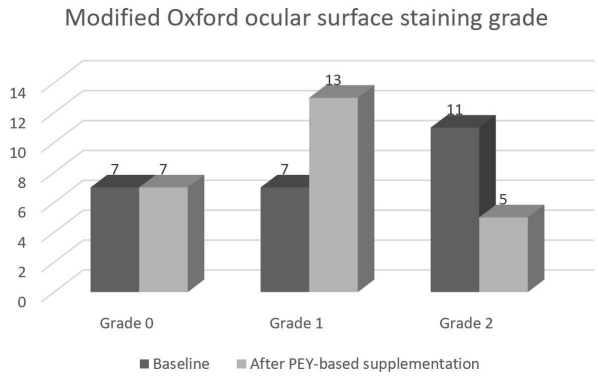

Figure 4. Ocular surface staining grading with fluorescein dye (using the modified Oxford ocular surface staining grading system) before (left) and after 45 days of oral supplementation with processed egg yolk capsules.

AUTHORSHIP

Nuno Moura-Coelho: writing of the original draft, writing review and editing, data analysis. *José Güell*: conceptualization, methodology, research design, writing of the original draft, supervision, validation. *Nuria Artells*: writing of the original draft, writing review and editing*. Renato Papa*: writing of the original draft, writing review and editing. *Felicidad Manero*: research design, data analysis, supervision, validation. *José M Benítez-del-Castillo*: conceptualization, methodology, research design, supervision, validation.

DISCLOSURES

The authors declare no conflicts of interest.

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