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Effect of a Mediterranean dietary pattern and Vitamin D levels on dry eye syndrome

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Abstract

Purpose—To evaluate the association between a Mediterranean dietary pattern (MeDi) and Vitamin D levels on dry eye syndrome (DES)

Design: Cross-sectional study.

Participants: Male patients seen in the Miami Veterans Affairs eye clinic with normal eyelid, corneal, and conjunctival anatomy were recruited to participate in the study.

Testing: Patients filled out the 2005 Block Food Frequency Questionnaire (FFQ) and the Dry Eye Questionnaire 5 (DEQ5) and underwent measurement of tear film parameters. Serum level of 25-hydroxy vitamin D was also measured.

Main outcome measures: Association between MeDi, Vitamin D levels and dry eye syndrome.

Results—247 men underwent DES testing. The mean patient age was 69 years (range 55 to 95). Using latent class analysis (LCA) to categorize the presence/absence of disease and quantify its severity, we found that adherence to the MeDi was positively associated with the risk both of having DES (odd ratio (OR) 1.25, 95% confidence interval (CI) 1.06–1.47) p=0.007) and with increasing disease severity. Vitamin D levels were not significantly associated with presence or severity of disease. However, higher levels of vitamin D were associated with decreased DES symptoms, with a −1.24 decrease in median DEQ5 score for every 10 unit increase in Vitamin D levels (p=0.01).

Conclusions—Adherence to the MeDi was not associated with a beneficial effect on DES. Higher vitamin D levels had a small, but favorable effect on DES symptoms.

Keywords

Dry eye syndrome; food frequency questionnaire; Mediterranean diet; Vitamin D

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Introduction

Dry eye syndrome (DES) is a prevalent condition, with symptoms that negatively impact the ability to work and function.[1–3] Given its frequency and morbidity, DES is a leading cause of visits to eye care clinics and has significant cost implications. Current dry eye treatments include topical lubrication, plugging of the lacrimal punctae, and topical anti-inflammatory therapy. As many patients have residual symptoms while on maximal medical therapy, new dry eye therapies are needed to improve the morbidity associated with disease.

DES is thought to have an inflammatory component as T cells are found in the conjunctivae of DES patients and elevated inflammatory cytokines (e.g. tumor necrosis factor alpha and interleukin 1, 6) are found in their tears.[4, 5] There is evidence that certain dietary manipulations may affect DES by affecting ocular surface inflammation. For example, anti-oxidant and omega-3 oral supplementations have been shown to improve tear film parameters and decrease ocular surface inflammation (as measured by HLA-DR) in patients with DES.[6–8] Beyond the study of isolated nutrients, there is increasing interest in understanding the relationship between dietary patterns and disease processes. For example, there has been much interest in the effects of a Mediterranean-style diet (MeDi) on systemic inflammation.[9] A MeDi diet includes a relatively high intake of fruits, vegetables, monounsaturated fat, fish, whole grains, legumes, and nuts, moderate alcohol consumption, and a low intake of red meat, saturated fat, and refined grains.

Studies have shown that MeDi may be a strong protective factor against all-cause mortality, coronary heart disease, and diabetes.[10] Furthermore, an inverse association has been found between adherence to MeDi and several subclinical markers of vascular disease risk including decreased insulin resistance and lower levels of inflammatory markers (e.g. C-reactive protein and interleukin-6).[10] There is a knowledge gap, however, on whether this dietary pattern has an effect on DES. There is biological plausibility that the MeDi may have an effect on DES given that ocular surface inflammation is seen in patients with disease and the MeDi has been shown to decrease systemic inflammation.

Another nutrient that has generated recent excitement is vitamin D, a fat soluble vitamin produced in the skin after exposure to ultraviolet light, and which occurs naturally in a small number of foods.[11] It is well known that vitamin D regulates serum calcium and phosphate levels and thereby has an important role in maintaining bone health.[11] Less well understood are its other functions which include modulation of immune function, reduction of inflammation, and involvement in epithelial cell health.[12] Low vitamin D levels have been found to be prevalent among older adults but its impact on health is unclear.[13] Observational studies have demonstrated associations between low vitamin D levels and peripheral vascular disease and Alzheimer’s disease.[14, 15] Furthermore, 25-hydroxyvitamin D was inversely correlated with the inflammatory marker soluble interleukin-2 receptor.[16] While no studies have evaluated the effect of vitamin D levels on DES, one study found that patients with Sjogren’s syndrome had slightly decreased 25-hydroxyvitamin D levels compared to a control population.[16]

The purpose of this study was to evaluate how adherence to a Mediterranean diet and vitamin D levels affected DES in an older male population. Furthermore, given data on the effect of omega 3 in women with DES, we aimed to evaluate how the intake of omega 3 affected DES parameters in our unique population. This information is important for clinicians and researchers alike as it increases knowledge on the potential usefulness of dietary modification and nutritional supplementation in DES.

Methods

Study Population

The Miami Veterans Affairs Institutional Review Board reviewed and approved the prospective examination of patients for this study, which was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all study participants.

Patients were recruited from the Miami Veterans Affairs (VA) eye clinic irrespective of their tear function status. Patients were not eligible to participate if they were female, under 50 years of age, or had any eyelid (e.g. lagophthalmos, ectopion), conjunctival (e.g. significant conjunctivochalasis, pterygium), or corneal (e.g. scarring, edema) pathology. Of note, patients with pinguecula were not excluded from the study. Further exclusion criteria included the use of contact lenses, ocular medication with the exception of artificial tears/ topical cyclosporine, ocular surgery within the last 3 months, HIV, Sjogren's syndrome, sarcoidosis, graft-versus host disease, or a collagen vascular disease.[17]

Data Collected

Each participant filled out a validated 2005 Block food frequency questionnaire (FFQ) and the five-item dry eye questionnaire (DEQ5)).[18] The full-length (110 food item) Block FFQ was selected as it is designed to estimate usual and customary intake of a wide array of nutrients and food groups for a 1 year recall period. The value of FFQ for assessing dietary composition has been documented[19], and offers a cost-effective method for determining nutritional intake, with minimal participant burden. The ocular surface examination consisted of: tear osmolarity (measured once in each eye) (TearLAB, San Diego, CA), tear breakup time (measured twice in each eye and averaged per eye) (range 0–15), corneal staining (punctate epithelial erosions (PEE), range 0–5), Schirmer's strips with anesthesia, and morphologic and qualitative eyelid and meibomian gland information. Morphologic information collected included the degree of eyelid vascularity (0 none; 1 mild engorgement; 2 moderate engorgement; 3 severe engorgement) and the presence of inferior eyelid meibomian orifice plugging (0 none; 1 less than 1/3 lid involvement; 2 between 1/3 and 2/3 involvement; 3 greater than 2/3 lid involvement). Meibum quality was graded on a scale of 0 to 4 (0 = clear; 1 = cloudy; 2 = granular; 3 =toothpaste; 4=no meibum extracted). Data was entered into a standardized database. Blood was also collected and serum levels of 25-hydroxy vitamin D was measured.

Statistical analysis

All statistical analyses were performed using SAS 9.3 (Cary, NC) statistical package. Descriptive statistics were applied to characterize tear film parameters in the population.

Mediterranean diet score—In this paper, we replicated the methodology used by previous groups to convert FFQ data into an ordinal score reflecting conformity to the MeDi pattern.[20, 21] In brief, the caloric intake (kilocalories) is regressed and the derived residuals of daily gram intake for seven categories is calculated (dairy, meat, fruits, vegetables, legumes, whole grains, and fish).[21] Individuals are assigned a value of 1 for each beneficial component (fruits, vegetables, legumes, cereals, and fish) whose consumption is at or above the sex-specific median, for each detrimental component (meat and dairy products) whose consumption is below the median, for a ratio of monounsaturated fats to saturated fats above the median, and for mild to moderate alcohol consumption (>0 drinks per week but ≤2 drinks per day over the previous year).[22] The diet score is the sum of the scores in the food categories (range, 0–9) with a greater score indicating greater adherence to a MeDi dietary pattern. The resulting diet score indicates how well an individual's diet corresponds to a traditional Mediterranean-style diet in relation to others in the study population.

Omega 3—The FFQ provided information on average daily intake of omega-3 and 6 fatty acids (per gram) and on omega-3 fatty acids from supplements (per gram).

Diagnosis of DES—We used latent class analysis (LCA), to determine whether a patient had DES (yes/no) and assigned an overall DES severity score (continuous variable from 0 (no disease) to 1 (most severe disease)).[23] Patients with a posterior probability score of greater than 0.5 were defined as diseased (42%) while those with scores less than 0.5 were defined as non-diseased (58%).[23] The association between dietary and nutrient data was also examined with respect to several tear film parameters including the presence of ocular surface symptoms (DEQ5 score), aqueous tear deficiency (ATD) (Schirmer's score) and meibomian gland dysfunction (TBUT and MG parameters). With regard to the latter, while TBUT can be altered by abnormalities in any tear film layer, studies have shown that it seems to mostly closely reflect abnormalities in the lipid layer.[24] The more severe measurement from either eye was used in all analyses.

Relationship between nutrition and DES—Uni-variable and multi-variable analysis were performed using both logistic regression analysis (for dichotomous DES outcome variables) and quantile regression analysis (for continuous DES outcome variables). The latter analysis reported how a one-step increase in the independent factor (diet, vitamin D levels) affected the median of the dependent factor (DES parameters). This latter analysis was performed due to the lack of normal distribution of the continuous DES-related variables. Two such models were evaluated: Model 1 was unadjusted, and model 2 was adjusted for age, ethnicity, total daily kilocalories consumed (N/A for the MeDi score which already accounts for total energy), smoking (past, current, or never), depression, PTSD, antidepressant medication use, and anti-anxiety medication use.

Results

Study population

Clinical data from 247 men with complete tear film parameter information were included in this analysis. Mean patient age was 69 years ± 8.9 (range 55 to 95). Sixty-nine percent of patients self- reported themselves as white (n=170) and 29% as black (n=71). Twenty-seven percent (n=66) self-reported themselves as being of Hispanic ethnicity.

MeDi and DES

Using latent class analysis (LCA) to define DES and quantify its severity, we found that adherence to the MeDi in the previous year (as assessed by the FFQ) increased both the risk of having DES (odd ratio (OR) 1.25, 95% confidence interval (CI) 1.06–1.47) p=0.007) and of having increased disease severity (Table 1). This seems to be have been driven by an association between the MeDi score and meibomian gland (MG) parameters. In a multi-variable analysis, a 1 point increase in MeDi score was associated with an 18% increased risk of a TBUT less than 5 and of an abnormal meibum quality (2 or greater). Similarly, a 1 point increase in MeDi was associated with a 19% increased risk of an abnormal corneal staining score (2 or greater). Of note, a higher MeDi score was associated with a higher (i.e. more healthy) Schirmer score (p=0.02). The MeDi was not associated with DES symptoms (as measured via the DEQ5 questionnaire).

When a sensitivity analysis was performed to examine which factors of the MeDi were driving the association, it was found that when we removed alcohol, vegetables, legumes, and fish individually from the score, the modified MeDi score (range 0–8) was no longer significantly associated with DES severity (by the LCA posterior probability score) (data not shown). Evaluating alcohol use in isolation, moderate alcohol use increased the risk of DES with a 2 fold increased risk of overall disease (OR=2.01, 95% CI=1.11–3.63, p=0.02). This was again mostly driven by meibomian gland parameters with a 2.14 fold increased risk of a TBUT score less than 5 (95% CI=1.20–3.80, p=0.01), and a 2.11 fold increased risk of corneal staining greater than 1 (95% CI=1.09–4.07, p=0.03), when adjusting for age and ethnicity.

Vitamin D and DES

Vitamin D levels were not significantly associated with most DES parameters, including presence of disease, disease severity, and aqueous deficiency parameters (Table 2). However, higher vitamin D levels were significantly associated with lower DES symptoms (−1.24 decrease for every 10 unit increase in vitamin D, p=0.01).

Omega-3 and DES

Daily intake and nutritional supplementation with omega 3 did not associate with most DES parameters, including overall presence of disease, disease severity, and aqueous and lipid deficiency parameters (Table 3). A 1 gram increase in omega-3 intake was associated with a 2.43 increased risk of severe dry eye symptoms (OR 2.43, 95% CI 1.01–5.82, p=0.047).

Discussion

There is much interest in understanding how diet influences ocular surface health and DES. While the Mediterranean diet has been found to improve systemic markers of inflammation, our findings do not support the hypothesis that this dietary pattern is protective against DES. In fact, in our cross-sectional study, patients who adhered to this diet had more severe disease. Several potential explanations for our findings can be postulated including (1) the MeDi is indeed not an ideal dietary pattern for control of DES, with the effect of alcohol counteracting the effect of other nutrients (2) patients with DES may have improved their diet in an effort to help alleviate their condition; (3) the results were confounded by unmeasured variables; or (4) the unexpected associations may have been observed due to chance. Unfortunately, as with any cross-sectional observational study, it is not possible to further differentiate between these possibilities.

While we did find a positive effect of vitamin D levels on DES symptoms, the effect was small and likely not clinically meaningful. Previous studies have found a beneficial effect of omega 3 on ocular health.[7, 8, 25, 26] Postulated mechanisms of omega 3 on the ocular surface include anti-inflammatory effects[8] and/or the modification of meibum properties.[27] One study of women with Sjogren’s syndrome found a difference in polar lipid profiles based on intake of omega-3.[28] Compared to these previous studies, we were not able to demonstrate a positive effect of omega 3 intake (both in food and supplements) on DES in our patients. As above, this may have been due to, among other things, patients with DES improving their diet, limitations with the FFQ, or unmeasured variables which confounded the results.

As with all studies, our work has limitations which need to be considered when interpreting its results. First, we measured tear parameters at one time point and DES is a disease known to have substantial temporal variation. Second, we recognize that all methods of dietary assessment are imperfect with potential sources of error including possible difficulties recalling food consumed over the past year, underreporting of unhealthy intakes and over-reporting of healthy foods. Moreover, the FFQ food list is finite and therefore may not fully account for inter-individual differences in the intake of certain nutrients. Lastly, some variables that may have confounded our results were not assessed such as socioeconomic status, caffeine intake, occupation, and exposure to sunlight. Despite these limitations, we did not find a beneficial effect of adhering to the MeDi on DES. Higher vitamin D levels had a small, but favorable effect on DES symptoms.

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Table 1

Effect of Mediterranean diet (assessed as continuous scale from 0–9) on dry eye syndrome

DES parameter	Uni-variable	Multi-variable[a]
Presence of disease[b] vs. absence Disease severity[b]	OR[c] 1.22 (95% CI 1.05–1.43), p=0.01 .0543, p=0.07[d]	OR 1.25 (95% CI 1.06–1.47), p=0.007 0.0498, p=0.03[d]
DEQ5, ≥12 vs. 11 and less DEQ5, continuous variable	OR 1.02 (95% CI 0.89–1.18), p=0.78 .0000, p=1.00[d]	OR 1.05 (95% CI 0.90–1.22), p=0.53 .2250, p=0.43[d]
Schirmer's, <5 vs. 5 and greater Schirmer's, continuous variable	OR 0.92 (95% CI 0.77–1.09), p=0.35 0.4000, p= 0.09[d]	OR 0.92 (95% CI 0.77–1.10), p=0.36 0.6163, p=0.02[d]
TBUT, <5 vs. 5 and greater TBUT, continuous variable	OR 1.17 (95% CI 1.01–1.35), p=0.03 −0.5000, p=0.11[d]	OR 1.18 (95% CI 1.01–1.38), p=0.04 −0.4545, p=0.06[d]
Osm, ≥326 vs. 325 and less Osm, continuous variable	OR 1.12 (95% CI 0.90–1.41), p=0.32 0.0000, p=1.00	OR 1.15 (95% CI 0.91–1.46), p=0.25 0.1132, p=0.88
Meibum quality, >1 vs. 0 or 1	OR 1.14 (95% CI 0.99–1.32), p=0.07	OR 1.18 (95% CI 1.01–1.38), p=0.04
Eyelid vascularity, >1 vs. 0 or 1	OR 1.06 (95% CI 0.89–1.26), p=0.51	OR 1.03 (95% CI 0.85–1.23), p=0.75
MG plugging, >1 vs. 0 or 1	OR 1.02 (95% CI 0.87–1.19), p=0.80	OR 1.00 (95% CI 0.85–1.18), p=1.00
Conjunctival staining, >1 vs. 0 or 1	OR 1.19 (95% CI 1.01–1.41), p=0.04	OR 1.19 (95% CI 1.00–1.41), p=0.05

DES=dry eye syndrome; TBUT=tear break up time; DEQ5=dry eye questionnaire 5; vs= versus; Osm=osmolarity; MG=meibomian gland; OR=odds ratio; CI=confidence interval

[a]Multivariable model controlled for age, ethnicity, smoking, depression, post-traumatic stress disorder, antianxiety medication use, antidepressant medication use.

[b]Latent class analysis used to determine presence of disease and severity. Severity scores ranged from 0 (no abnormality) to 1 (most severe abnormality).

[c]Odds ratios calculated using logistic regression analysis to determine the association between the Mediterranean diet (MeDi) and binary DES outcome variables. An OR greater than 1 signifies an increased risk of disease.

[d]Quantile regression analysis reports how a one-step increase in MeDi affected the median of the dependent DES parameters. For example, a 1 point increase in the MeDi score increased the median DES disease severity by 0.05.

Table 2

Effect of vitamin D levels (per ng/mL) on dry eye syndrome

DES parameter	Uni-variable	Multi-variable[a]
Presence of disease[b] vs. absence Disease severity[b]	OR[c] 1.01 (95% CI 0.98–1.03), p=0.43 0.0008, p=0.91[d]	OR 1.00 (95% CI 0.97–1.03), p=1.00 −0.0007, p=0.89[d]
DEQ5, ≥12 vs. 11 and less DEQ5, continuous variable	OR 0.98 (95% CI 0.95–1.00), p=0.12 −0.1364, p=0.01[d]	OR 0.98 (95% CI 0.95–1.00), p=0.12 −0.1236, p=0.01[d]
Schirmer's, <5 vs. 5 and greater Schirmer's, continuous variable	OR 1.01 (95% CI 0.98–1.05), p=0.57 0.0476, p=0.53[d]	OR 1.01 (95% CI 0.97–1.04), p=0.58 0.0455, p=0.53[d]
TBUT, <5 vs. 5 and greater TBUT, continuous variable	OR 0.99 (95% CI 0.97–1.02), p=0.43 0.0882, p=0.14[d]	OR 0.99 (95% CI 0.96–1.02), p=0.52 0.0509, p=0.34[d]
Osm, ≥326 vs. 325 and less Osm, continuous variable	OR 1.02 (95% CI 0.98–1.06), p=0.39 0.7317, p=0.57	OR 1.01(95% CI 0.97–1.06), p=0.59 1.0485, p=0.34
Meibum quality, >1 vs. 0 or 1	OR 1.00 (95% CI 0.97–1.03), p=1.00	OR 1.00 (95% CI 0.97–1.03), p=1.00
Eyelid vascularity, >1 vs. 0 or 1	OR 1.04 (95% CI 1.01–1.08), p=0.02	OR 1.05 (95% CI 1.01–1.08), p=0.004
MG plugging, >1 vs. 0 or 1	OR 1.01 (95% CI 0.98–1.03), p=0.43	OR 1.01 (95% CI 0.98–1.04), p=0.52
Conjunctival staining, >1 vs. 0 or 1	OR 0.99 (95% CI 0.96–1.02), p=0.41	OR 0.98 (95% CI 0.95–1.02), p=0.33

DES=dry eye syndrome; TBUT=tear break up time; DEQ5=dry eye questionnaire 5; vs. versus; Osm=osmolarity; MG=meibomian gland; OR=odds ratio; CI=confidence interval

[a]Multivariable model controlled for age, ethnicity, smoking, depression, post-traumatic stress disorder, antianxiety medication use, antidepressant medication use.

[b]Latent class analysis used to determine presence of disease and severity. Severity scores ranged from 0 (no abnormality) to 1 (most severe abnormality).

[c]Odds ratios calculated using logistic regression analysis to determine the association between vitamin D levels and binary DES outcome variables. An OR greater than 1 signifies an increased risk of disease.

[d]Quantile regression analysis reports how a one-step increase in vitamin D levels affected the median of the dependent DES parameters. For example, a 1 point increase in vitamin D levels increased the median DES disease severity by 0.0008.

Table 3

Effect of omega 3 fatty acids (per gram) on dry eye syndrome

DES parameter	Uni-variable	Multi-variable[a]
Presence of disease[b] vs. absence Disease severity[b]	OR[c] 1.27 (95% CI 0.55–2.97), p=0.58 0.0566, p=0.76	OR 1.37 (95% CI 0.56–3.36), p=0.49 0.0856, p=0.54
DEQ5, ≥12 vs. 11 and less DEQ5, continuous variable	OR 2.21 (95% CI 0.98–5.02), p=0.06 2.3617, p=0.08	OR 2.43 (95% CI 1.01–5.82), p=0.047 1.5090, p=0.35
Schirmer's, <5 vs. 5 and greater Schirmer's, continuous variable	OR 1.21 (95% CI 0.48–3.05), p=0.69 −1.0254, p=0.62	OR 1.53 (95% CI 0.59–3.96), p=0.38 −0.6036, p=0.74
TBUT, <5 vs. 5 and greater TBUT, continuous variable	OR 0.89 (95% CI 0.41–1.96), p=0.77 0.2778, p=0.89	OR 0.87 (95% CI 0.38–2.01), p=0.74 0.8075, p=0.63
Osm, ≥326 vs. 325 and less Osm, continuous variable	OR 1.04 (95% CI 0.28–3.87), p=0.95 −0.6075, p=0.83	OR 1.69 (95% CI 0.31–9.12), p=0.54 −0.5553, p=0.87
Meibum quality, >1 vs. 0 or 1	OR 0.98 (95% CI 0.45–2.13), p=0.96	OR 1.06 (95% CI 0.48–2.39), p=0.89
Eyelid vascularity, >1 vs. 0 or 1	OR 0.87 (95% CI 0.33–2.32), p=0.78	OR 0.81 (95% CI 0.28–2.33), p=0.70
MG plugging, >1 vs. 0 or 1	OR 0.81 (95% CI 0.34–1.95), p=0.64	OR 0.91 (95% CI 0.37–2.20), p=0.84
Conjunctival staining, >1 vs. 0 or 1	OR 1.12 (95% CI 0.46–2.75), p=0.81	OR 1.44 (95% CI 0.55–3.76), p=0.46

DES=dry eye syndrome; TBUT=tear break up time; DEQ5=dry eye questionnaire 5; vs. versus; Osm=osmolarity; MG=meibomian gland; OR=odds ratio; CI=confidence interval

[a]Multivariable model controlled for age, ethnicity, total daily kilocalories, omega-6 intake, smoking, depression, post-traumatic stress disorder, antianxiety medication use, antidepressant medication use.

[b]Latent class analysis used to determine presence of disease and severity. Severity scores ranged from 0 (no abnormality) to 1 (most severe abnormality).

[c]Odds ratios calculated using logistic regression analysis to determine the association between omega 3 levels and binary DES outcome variables. An OR greater than 1 signifies an increased risk of disease.

[d]Quantile regression analysis reports how a one-step increase omega-3 levels affected the median of the dependent DES parameters. For example, a 1 point increase in omega 3 levels increased the median DES disease severity by 0.06.