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Cytokine/Chemokine Expression in Reflex Tears from Employers Exposed to Computer Screens in a Healthy Office Environment

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Abstract

Objective: To inform employees exposed to computer screens (CSs) about the risk of dry eye disorders (DEDs) and how to prevent them.

Methods: From a total of 800 public-sector employees, eighty-eight CSs users were randomly selected to participate in an interview and an ophthalmic examination, and compared to thirty-six healthy volunteers no CSs users including family members, nurses and assistants. Environmental conditions in the workplace were documented. Reflex tear samples were collected simultaneously from both eyes and were later subjected to a multiplexed particle-based flow cytometry assay. A specific set of immune response biomarkers was analyzed.

Results: The mean age was 52.17 (5.17) years; 27% were men and 73% women. DEDs were newly diagnosed in 86% of the participants. Mean CS exposure was 4.8 (1.27) hours. Environmental workplace conditions complied with general standards. Schirmer test results and blinking frequency were pathologic in up to 2/3 of the employers exposed to CSs. Immune response biomarkers were detected in 90% of tear samples. Compared with records of healthy, non-exposed control subjects in a pre-existing database, tear samples of the participants exposed to CSs had significantly higher levels of interleukins (IL) (IL1B, IL2, IL6, IL8), GM-CSF, IFG, and VEGF.

Conclusion: Employee exposure to CSs was a major risk factor for DED, being inflammation a main contributor to ocular surface pathogenesis.

Keywords: Dry eyes; Computer screen; Employee; Immune response; Tears

Introduction

Temperature, humidity, wind, fumes, pollution, as well as air speed, CO_2 concentration, and light intensity play pivotal roles in vision outcomes [1]. Office employees spend many hours in front of a computer screen (CS). Adverse effects of such exposure have been referred to as computer-vision syndrome (CVS) [2]. In this context, computer users often present ocular signs and symptoms such as itchiness, soreness, foreign body sensation, irritation, photophobia, redness, eye strain, tired eyes, blurred vision blurred, and double vision [3-5]. A search of the scientific literature led us to several studies performed with subjects exposed to CSs in office environments [6-8], but there have been no reports of integrated data about working conditions, CSs exposure, external and internal risk factors, and inflammatory molecules related to ocular surface dysfunction.

Ocular surface dysfunction refers to complex conditions involving the eyelids, cornea, conjunctiva, lacrimal glands, and tear film [1-5]. However, the term *dry eye disorder/s* (DED/s) has been more recently introduced to better distinguish the ocular surface dysfunction that induces tear film impairment and dry eye [3].

We attempt to shed light on ocular surface dysfunction and working conditions to improve awareness of workers and help them prevent chronic DEDs and visual impairment. For reaching this objective in a better way we have determined: 1) the main risk factors for DEDs; 2) the prevalence and severity of DEDs, and the relationship between CS exposure duration and DED severity; and 3) the expression of biomarkers of immune response in tear samples and its relationship to DED severity.

Methods

Men and women were randomly selected from among the employees of the General Treasury of Social Security in Valencia, Spain. Inclusion and exclusion criteria are reflected in Table 1. Eighty-eight CSs users and thirty-six CSs non users were enrolled when signing the informed consent. The Ethics Committee of the Ophthalmic Research Unit "Santiago Grisolia" Center approved the present study (2012) that was conducted according to Declaration of Helsinki principles.

We conducted personal interviews and assigned scores for

inclusion criteria	Exclusion criteria
Unawareness of ocular surface disorders	Previous diagnosis of ocular surface disorders
Ability to participate	Sjögren syndrome
	Use of contact lenses
	Other ocular disorders
	Use of eye drops other than artificial tears
	Recent history of ocular laser treatment/ophthalmic SURGERY
	Systemic diseases and general treatments
	Atopy or allergic disorders
	No ability to participate

Table 1: Inclusion and exclusion criteria for the study participants.

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objective and subjective criteria (ocular surface disease index [OSDI] questionnaire). The questionnaire sections are divided into three main questions:

1. Have you experienced photophobia, a gritty feeling, soreness, or blurred vision during the last week?
2. Have your eye problems limited you in reading, driving at night, computer work, or watching TV during the last week?
3. Have your eyes felt uncomfortable in windy or dry situations or because of air conditioning during the last week?

Interviewers paid special attention to the comments of the participants regarding lifestyle and eye conditions.

In addition, a systematized ophthalmic examination was performed on all participants as follows: value of the eyelid Schirmer test, slit lamp examination for the eye adnexa and anterior eye segment and corneal surface details with fluorescein. Examiners completed a full sheath to enclose all data, and were advised to strictly follow the study protocol. Primary outcomes of the ophthalmic examination measures for determining the ocular surface status were the Schirmer test and fluorescein ocular surface details, as well as assessment of blinking frequency (near and far); the secondary measure was dry eye symptoms. Other signs and symptoms of DEDs were evaluated based on self-reports. Depending on clinical manifestations, patients were considered to be free of DEDs or to have mild, moderate, or severe DEDs.

Reflex tear samples were obtained with a Pasteur micropipette from the inferior lid cul-de-sac of both eyes by gentle rubbing, as shown in the Figure 1. The expression of a set of immune mediators was assayed with the Multiplex System (Luminex® R-200, Luminex Corporation; Austin, TX, USA). Polystyrene beads coupled covalently to specifically directed antibodies (human cytokine/chemokine panel) were allowed to react with 20–30 μL of each tear sample containing an unknown amount of cytokines, or with a standard solution containing a known amount of cytokines, at room temperature for 1 hour, according to the manufacturer's instructions. The following cytokines/chemokines were analyzed: interleukin (IL)-1α, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, and IL-12; tumor necrosis factor alpha; vascular endothelial growth factor (VEGF); granulocyte-macrophage colony-stimulating factor; and interferon gamma, as previously described [9]. Briefly, a series of washes was carried out to remove unbound proteins. Then, a biotinylated detection antibody specific for a different epitope on the cytokine was added to the beads and incubated at room temperature for 30 minutes. Streptavidin-phycoerythrin (which binds to the biotinylated detection antibodies), was used to detect the reaction mixture. The flow-based Bio-Plex® (Bio-Rad Laboratories; Hercules, CA, USA) suspension array system was used to identify and quantify each antigen–antibody reaction. Identification of the assayed molecules was based on bead color and fluorescence, using fluorescently labeled reporter molecules associated with each target protein. Unknown cytokine/chemokine concentrations were calculated automatically by the Bio-Plex® Manager software (Bio-Rad Laboratories) using a standard curve derived from a recombinant cytokine standard. Levels of these molecules were corrected for the initial total protein concentration of each tear sample during analysis. We previously created a database with values for the above set of immune response molecules [9,10]. Values for expression of molecules in samples obtained from non-exposed, healthy controls were used for comparison with data from employees participating in the current study. Data are reported as means (standard deviations) of two or three values and expressed in picograms per milliliter per milligram.

Special attention was paid to the workplace conditions in the office that were evaluated by the following homologized systems: heat stress monitor, indoor air quality (IAQ), Microtherm IAQPROBE DAE 504002, luxometer GOSSEN MAVOLUX 5032 C/B nº serie 0C60759, and CO_2 concentration analyzer Ex 2000 Oldham/CO_2.

Demographic, lifestyle, working conditions, environmental, clinical, and molecular data were independently gathered. We used nonparametric Mann–Whitney U test to compare two independent sample groups with Statistical Package for the Social Sciences (SPSS) software (v15.0; SPSS Inc; Chicago, IL, USA). A value of $p \leq 0.05$ was considered an indication of a statistically significant difference between groups.

Results

The participants' mean age was 52.17 (5.17) years in the CSs exposed individuals and 50.10 (12.24) years in the non-exposed controls; 26.82% were men and 73.17% women in the CSs exposed group vs. 32% and 68% of the controls. Regarding ethnics, all participants were Caucasian.

Of the CCs exposed group 96% wear glasses all the time vs. 62% of the controls.

DEDs were newly diagnosed (based on the OSDI questionnaire and ophthalmic examination) in 86% of the CSs exposed subjects. Among these, 29.26% had mild DED and 70.73% had moderate DED. No severe DED were detected within this group of participants. Their main complaints were itchiness, dryness, tired eyes, red eyes, and blurred vision. Mean exposure time to computer screens was 4.8 (1.27) hours (8 hours maximum). However, no significant CSs exposure was recorded within the healthy volunteers.

The most significant molecules in tear samples from the mild DED group were IL-8 (P=0.001) and IL-12 (p=0.031). The outstanding immune mediator in samples from the moderate DED group was IL-6 (p=0.032).

Environmental conditions detected in the workplace (dry temperature, relative humidity, light intensity, CO_2 parts per million) were within normal ranges at all times (Table 2).

Background cytokine concentrations were subtracted from the cytokine concentrations detected in the tears. The standard curves for both the kit assay and the extraction buffers were similar for the 12 analyzed molecules. In up to 90% of the sampling procedures, the volume of tears obtained was sufficient.

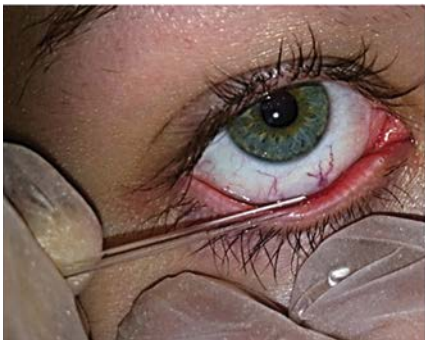

Figure 1: Illustrating the tear reflex sample collecting method.

The tear samples showed a wide variety of expression levels of the set of assayed molecules. Precision, as measured by the Luminex multianalyte profiling bioassay system (Luminex Corporation), was acceptable. In fact, CS-exposed study participants had significantly higher levels of cytokines/chemokines than non-exposed controls (Table 3).

Discussion

During interviews, the main complaints were itchiness, dryness, tired eyes, red eyes, and blurred vision, similar to results of other studies [11-13]. Considering that the mean CS exposure time was 4 hours, these signs and symptoms were similar to those in several reports of video-terminal users [11-16]. Interestingly, 86% of our participants had mild or mild-to-moderate dry eyes not previously diagnosed.

Cytokines are extracellular signaling proteins [17]. The expression of cytokines/chemokines such as regulated on activation, normal T-cell expressed and secreted, may underlie the clinical manifestations observed in some DEDs patients. In fact, tear samples from the DEDs affected subjects displayed significantly higher expression levels of immune response molecules. Moreover, the cytokine profile seen in chronic mild DED patients was different from that observed in chronic moderate DEDs. Concentrations of IL-8 and IL-12 released from macrophages in the mild DED group were significantly higher than those from healthy controls and from those in patients with moderate DEDs. Those molecules play an important role in the inflammation processes underlying airway dysfunction [18-20], as well as in response to smoking habits [21]. Nevertheless, the role of these cytokines needs to be defined and there is a potential for anticytokine therapy in chronic ocular surface disease.

In addition, in the moderate DED patients there were an upregulation of IL-6. It has been suggested that IL-6, a major pro-inflammatory cytokine, is, by itself or in combination with other similar molecules, a potential biomarker of DED progression [9,10,22-27].

Under the current study's environmental conditions, CSs exposure induced a significant increase in the immune mediator tear levels. In a similar manner it has also been described the effects of oxidant air pollutants on the respiratory system [18]. Although the importance of immune mediators in ocular surface anomalies is still growing, this study provides enough evidence that the tear expression profiles of inflammatory mediators in the mild and moderate phases of the DEDs can be useful for further understanding of the complex DEDs pathology.

Data strongly indicate that screening employees exposed to CSs, with or without eye signs or symptoms, may be useful. Answers to the three sets of questions in Table 4 can shed light on the status of the ocular surface, regardless of the subject's knowledge of eye disorders.

DEDs and their downstream effects contribute negatively to quality of life. This confers special relevance to the care process, as previously recognized [20-26]. The following measures are recommended for employees exposed to CSs for ≥ 4 hours: 1) Use ample, uncluttered screens with flexible contrast and brightness and establish a distance of 50–80 cm from the CS, with the CS slightly below the plane of the eyes. 2) To prevent reflections and glare, avoid positioning the CS in front of or behind a light source or window. 3) Adjust environmental light to 200–500 lux, depending on the type of work. 4) Close eyes for a few seconds after ≤ 30 minutes of CS exposure. 5) Squint hard 5 times after ≤ 1 hour of continuous CS exposure, and increase blinking frequency. 6) Look away from the computer and toward the infinite after ≤ 2 hours of CS exposure. 7) Without moving the head, direct eyes up, down, right, then left 5-10 times (midway through work period and again at the end of work period). 8) Whenever possible use glasses and avoid contact lenses. 9) Use artificial tears or hydrating eye drops whether suffering dryness or not. 10) Take supplements with antioxidants and omega-3 fatty acids, which help in maintaining the oxidative and antioxidant balance for the ocular surface and promote healthy eyes and vision.

Environmental Parameters	Measurements
Air Speed m/s	0.11 ± 0.031
Relative Humidity %	32.673 ± 5.13
Dry Temperature ºC	24.56 ± 0.60
Light Intensity Lux	500
CO2 parts per million	2370.71 ± 646.89

Environmental parameters in the work place (measured by homologized systems)

Table 2: Environmental parameters in the workplace.

Set of immune mediator molecules assayed in tear samples	GECS (Group exposed to computer screens)	GC (Group of non exposed to computer screens)	p valor*
IL1β	36,40 ± 35,30	10,98 ± 15,42	0.00001
IL-2	0,67 ± 0,36	3,91 ± 1,21	0.034
IL-6	28,10 ± 71,7	13,16 ± 8,71	0.05
IL-8	1138, 47 ± 915,45	398,75 ± 270,43	0.00001
IL-10	0,59 ± 0,69	4,20 ± 1,51	0.00001
GM-CSF	2,96 ± 2,58	7,60 ± 3,24	0.00001
IFγ	0,26 ± 0,43	2,077 ± 0,67	0.00001
VEGF	1367,13 ± 591,51	542,29 ± 276,73	0.00001

Table 3: Expression levels of immune mediators in tear samples from employees exposed to computer screens. Data are means (standard deviations) of two values and are expressed in picograms per milliliter per milligram. Tear expression levels of immune mediators in employers exposed to CS. Data are mean ± standard deviation for two/three determinations, expressed in picograms per milliliter per milligram.

Usually I become aware of my eyes when exposed to:	In general, I resent of my eyes with the following symptoms:	I try to meliorate my eye disturbing sensations by:
Sunlight	Dryness	Coliriums
Brightness	Soreness	Home remedies
Wind	Itchiness	Tear substitutive eye drops
Heaters/Ventilators	Tired eyes	Saline solutions
Air Conditioning	Foreign body sensation	Vitamin eye drops
Fumes/Pollution	Photofobia	Antioxidant oral supplementation
Smoke	Burning	Essential fatty acid supplementation
Tv/Computer Screens	Redness	Clossing eyes
Reading	Blurred vision	Restricting activities
Driving at night	Visual loss	Nothing
Total Score 1st Column	*Total Score 2nd Column*	*Total Score 3rd Column*

Table 4: Awareness of the integrity of the ocular surface among employees exposed to computer screens: 30-item self-scored questionnaire for adults. *Convert each response to numerical data: mark each affirmative answer 1 and each negative answer 0. Visit an eye doctor if you have a sum of 4 or more in each of the three columns (or a global score of 12 or more)*. Being aware of the integrity of the ocular surface in people exposed to computer screens during the working time. 30-item self-scoring questionnaire for adults. Converting each response to numerical data as follows: each affirmative answer has to be marked with 1 while the negative ones as 0. Ranking 4 or more in each of the three columns (or obtaining a global score of 12 or more) it can be convenient to visit an eye doctor.

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