1. Excellence, State-of-the-art and Objectives

Introduction

Globally, at least 2.2 billion people have a vision impairment or blindness, of which at least 1 billion have a vision impairment that could have been prevented or has yet to be addressed [1]. A significant percentage of the world population suffers from an assortment of eye diseases. The majority of them have a prevalence rate that increases in older age. Eye diseases such as cataract, glaucoma and macular degeneration at their final stage frequently lead to blindness in many developing countries and they remain the primary cause of reduced life quality.

Glaucoma is a progressive optic neuropathy, characterized by loss of retinal ganglion cells (RGCs), and associated morphological changes to the optic nerve and retinal nerve fiber layer (RNFL). A major challenge in the management of glaucoma is how to best determine severity of disease and estimate the rate of progression. Although dry eye syndrome (DES) is not a threat to vision, however it is the most common cause of eye discomfort, with 68% of people aged over 60s to report DES-related symptoms and discomfort [2]. Unfortunately, there have been no known preventative treatments in the past. Surgery, laser and injectable treatments, although effective, are still expensive and invasive. In industrialized societies, patients, medicine doctors, researchers, nutritionists and biochemists are in search of vitamins and nutrients to prevent AMD, cataract, dry eye syndrome (DES) and glaucoma [3].

Although, Selye since 1956 and later Holmes and Rahe in 1967, confirmed that oxidative stress is defined as the response of an organism to a threatening stimulus in order to regain homeostasis, only after 1985 the concept of oxidative stress was formulated [4, 5]. Organic antioxidants that cause oxidative stress include byproducts of endogenous and exogenous processes that include oxygen and nitrogen [6, 7]. The majority of free radicals in cells are generated by mitochondrial oxidative phosphorylation, through the leakage of electrons from the electron transport chain [8, 9]. Substances with antioxidant activity are required to treat oxidative stress.

Concentrations of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in moderate levels are crucial for various physiological processes within the human body, their overproduction leads to oxidative stress, defined as the imbalance between the production and accumulation of ROS and the ability of the body to neutralize and eliminate them. In the brain, oxidative stress exhibits significant effects, due to its increased metabolical activity and limited cellular regeneration. Thus, oxidative stress is a major factor in the progressive loss of neurons structures and functions, leading to the development of severe neurodegenerative disorders [17]. Nutrition plays an important role in neuroprotection as recently shown by epidemiological and biochemical studies which identified food components as promising therapeutic agents. Neuroprotection includes mechanisms such as activation of specific receptors, changes in enzymatic neuronal activity, and synthesis and secretion of different bioactive molecules. All these mechanisms are focused on preventing neuronal damage and alleviating the consequences of massive cell loss [18].

The most common exogenous antioxidant compounds include vitamins, phenolic compounds, and carotenoids. Vitamin E is the most effective chain-breaking, lipid-soluble antioxidant in cellular membranes [19] and is one of the major scavengers of radical-oxygenated species in nervous cells [20]. It traps free radicals and breaks the chain reaction, preventing the propagation of lipid peroxidation. This reaction produces a-tocopheroxyl radical, which requires ascorbate for its regeneration back to reduced Vitamin E [19, 21]. Vitamin E is taken from the diet, incorporated into lipoproteins, and delivered systemically. Further, have been successfully tested in several *in vitro* and in animals models studies in order to improve aging-related process [22, 23, 24].

1.1. Proposal objectives and challenges

In this context, recent years have witnessed tremendous advancements in the field of antioxidant therapies, with a special emphasis for neuroprotection. The aim of this research is to evaluate the neuroprotective relationship of α-tocopherol in glaucoma patients and the number of retinal ganglion cells (RGCs) of the optic nerve. The need to study the relationship between glaucoma and vitamins stems from the fact that glaucoma is the leading cause of irreversible blindness, almost half of all glaucoma cases are undiagnosed and the prevalence increases over time [25, 26].

This makes it necessary to investigate whether vitamins have a preventative effect on glaucoma or slow the progression of the disease. Several studies have suggested that diet may have an effect on IOP, the only risk factor for glaucoma that can be cured, or on glaucoma caused by oxidative stress. Oxidative stress occurs when more active oxygen species are formed and can then be manipulated by the cell's antioxidant capacity. This leads to damage to the ocular fluid outflow system, trabeculum, resulting in increased IOP and eventually loss of retinal ganglion cells [26, 27].

In addition, a low ophthalmic (in aqueous humor) or systemic antioxidant capacity is associated with a more severe loss of visual field in glaucoma [28, 29, 30]. Although several studies have been conducted on the association of vitamins with glaucoma, it is often observed that the results are conflicting, with health professionals and patients often doubting the effect of vitamins on glaucoma. The human body possesses an inherent antioxidant defense mechanism which aims to prevent the reaction between free radicals and biological compounds, where the exogenous administration of antioxidative compounds is fundamental. Several dietary antioxidants have been investigated for their neuroprotective effects in the treatment of neurodegenerative disorders, but still there is essential an improved and robust design of new research .

1.2. State-of-the-art & Innovation

In 2018, a systematic review and meta-analysis was performed to determine the association of vitamins with glaucoma. In this review, the quality of the studies was evaluated, the aggregate size of the result was calculated and the heterogeneity between the studies was interpreted. A total of 629 articles were identified, of which 36 were included in the systematic review. The meta-analysis included five articles (940 cases of open-angle glaucoma (OAG) and a total of 123,697 patients) [31].

Vitamin E is considered important for its antioxidant activity. A total of six studies to date have linked the levels of vitamin E to glaucoma in the blood. One study reported lower levels of vitamin E plasma in the POAG group. Another study found no statistically significant association [32] and two other studies found elevated serum vitamin E levels in patients with glaucoma [33, 34]. For normal blood pressure (NTG), one study showed lower levels of vitamin E plasma in patients with NTG [35], while other studies found no difference in plasma levels of vitamin E among patients with NTG [36, 37, 38] . In terms of aqueous humor, lower levels of vitamin E have been reported in patients with glaucoma and both open and closed angle [39]. Studies on vitamin E intake through diet and its association with open-angle glaucoma have not revealed significant correlations [39, 40, 41].

The evidence however, about the neuroprotection relationship of a-tocopherol in glaucoma patients remains insufficient and controversial. Conclusions are not clear due to the absence of well-designed research.

1.3. Scientific and social impact

Vision is vitally important to every individual's communication, physical health, independence and mobility, social engagement, educational and employment opportunities, socioeconomic status, and performance of daily activities, such as reading, driving a car, and caring for family members [42, 43, 44, 45, 46, 47, 48, 49].

Untreated vision impairment can lead to a progressive inability to participate in family, social, and community activities and is associated with a higher prevalence of chronic health conditions, death or falls and injuries, social isolation, depression, and other psychological problems [50, 51, 52a,b, 53, 54, 55, 56, 57]. The financial impact of chronic vision loss on individuals and society is substantial (direct expenses for diagnosis and treatment, indirect expenses for governments and other healthcare providers). On the other hand, low cost solutions such as targeted nutrition possibly will prevent, stabilize or reduce the progression of eye neurodiseases, resulting in saving resources and making public health more sustainable and provide more quality in patients' life.

2. Methodology and Implementation

2.1. Research Methodology

Purpose: Since previous studies have shown increased blood levels of Vitamin E, which helps antioxidant shielding of nerve tissue, whilst reducing IOP, the aim of the research is to evaluate the neuroprotective relationship of α-tocopherol in glaucoma patients and the number of retinal ganglion cells (RGCs) loss of the optic nerve, as well as the progression of the disease.

Imaging and Diagnosis Tools: 1) Humphrey 745 I field analyzer, 2) Nidek OCT Lite (RNFL) analysis, 3) HPLC method, Vitamin E in Plasma.

Type of Study: Case-control.

Human subjects Research: Healthy, Glaucomatous and Suspected Glaucomatous eyes.

Recommended treatment: α-tocopherol tablets 400IU/day (180mg), Re-examination every three and six months.

Selection Criteria: All participating patients will undergo ophthalmological, optometric and blood examinations.

Exclusion criteria: Cataract, blurring of transparent media, pathological conditions such as AMD, diabetes, nerve diseases, all kinds of injuries inside or outside the eye, refractive errors, strabismus, anisometropia and anisoconjunctivitis, etc. Performing a Medical history Record, subjects declare any pathological blood disease, anemia and leukopenia, adhesion problems and that may affect the concentration of vitamin E in the blood, will be excluded.

Subjects will be also excluded if they present with a best-corrected visual acuity less than 6/12, spherical refraction outside 5.0 diopters and/or cylinder correction outside 3.0 diopters, or any other ocular or systemic disease that could affect the optic nerve or the visual field.

At each visit during follow-up subjects will undergo a comprehensive ophthalmologic examination including review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, gonioscopy, dilated fundoscopic examination, stereoscopic optic disc photography, and automated perimetry using the Swedish interactive threshold algorithm (SITA Standard 24-2). Only subjects with open angles on gonioscopy will be included.

2.1.1. Ethics Statement

All patients who agree to participate in the research, before any other action, will be given an explanatory booklet on the purpose and terms of the research, for the protection of medical confidentiality and sensitive personal data as well as a form / statement that have been informed of the explanatory note and agree without any reservation to participate in this research, according to Helsinki's statement for research involving human subjects and the approval of the Ethics by the Ethics Committee of the University of West Attica.

2.1.2. Description of Study Population

Two groups, glaucomatous patients and a healthy control group will comprise the Study Population. Glaucoma patients will be recruited from the patients of at the 2nd Department of Ophthalmology Clinic, Athens University - "ATTIKON Hospital". In glaucomatous group, glaucoma will be defined by the presence of a repeatable visual field test on the 24-2 program of the Humphrey visual field analyzer (Carl Zeiss Meditec, Inc., Dublin, California, USA). An abnormal visual field result could be defined as having a pattern standard deviation (PSD) outside the 95% confidence limits or a glaucoma hemifield test (GHT) result outside the reference range. Glaucomatous optic neuropathy could also be defined by the presence of neuroretinal rim thinning or RNFL defects on masked stereo- photograph assessment. OHT will be defined as an intraocular pressure (IOP) greater than 21 mmHg in the presence of a healthy-appearing optic disc without a repeatable abnormal visual field result. Healthy eyes are defined eyes with intraocular pressure of 21 mmHg or less with no history of increased IOP and no visual field abnormalities.

2.1.3. Standard Automated Perimetry

All patients should undergo SAP testing using the SITA-standard 24- 2 strategy every 30 days. Visual fields with more than 33% fixation losses or false-negative errors, or more than 15% false-positive errors will be excluded. The only exception may be the inclusion of visual fields with false-negative errors of more than 33% only when the field may show advanced disease (MD worse than 212 dB). Visual fields exhibiting a learning effect (i.e., initial tests showing consistent improvement on visual field indexes) will also be excluded. Visual fields will further be reviewed for the following artifacts: lid and rim artifacts; fatigue effects; inappropriate fixation; evidence that the visual field results were due to a disease other than glaucoma (such as homonymous hemianopia); and inattention.

2.1.4. Optical Coherence Tomography

Subjects will also undergo time domain-OCT (TD-OCT) with dilated pupils using the Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, California, USA). [15] The fast RNFL algorithm will be used to obtain RNFL thickness measurements. Three images should be acquired from each subject, with each image consisting of 256 A-scans along a 3.4-mm diameter circular ring around the optic disc. The average parapapillary RNFL thickness (360-degree measure) will be calculated automatically by the software and will be used in the study. RNFL Scans will also be evaluated as to the adequacy of the segmentation algorithm for detection of the RNFL. Only scans without obvious RNFL segmentation failure will be included in the study. Good-quality scans should have a focused image of the ocular fundus, signal strength of more than 7, and the presence of a centered circular ring around the optic disc.

2.1.5. Retinal Ganglion Cell Estimation

Estimates of RGC counts will be obtained using formulas based on previous work by Harwerth and colleagues [9] on the development and validation of a model-linking structure and function in glaucoma. Based on experimental studies in monkeys, the above authors derived an empirical model relating measurements in OCT to histological RGC counts as a function of RNFL thickness. The model considers the effect of aging in the axonal density and the effect of disease severity on the relationship between the neuronal and non-neuronal components of the RNFL thickness estimates obtained by OCT. To derive the total number of RGC axons from the global RNFL thickness measurement obtained by OCT (RGC), one can apply the following formulas:

$$d = (-0.007x \text{ age}) + 1.4$$

$$c = (-0.26x \text{ MD}) + 0.12$$

$$a = \text{average RNFLthickness} \times 10870 \times d$$

$$RGC = 10^{\wedge}(\{[\log10 (a)] \times 10\text{-}c\} \times 0.1)$$

In the above formulas, d corresponds to the axonal density (axons/ mm2), c is a correction factor for the severity of disease to take into account remodeling of the RNFL axonal and non-axonal composition. The variable a corresponds to the number of axons passing toward the optic disc at the point of the OCT circumference.

After estimates of RGC will be obtained, a linear regression model will be developed to relate the estimated number of RGCs to age and optic disc area in the healthy population. The purpose is to develop a model to predict the expected number of RGCs according to age and optic disc area. To avoid model over fitting, the regression parameters will be obtained using only half of the normal eyes (development sample). After the expected number of RGCs will be calculated for each eye, the estimated percentage of remaining RGCs will be obtained by dividing the estimated number of RGCs by age-corrected expected RGC estimates:

$$\text{Percent RGC} = \text{Actual RGCcount/ Expected RG Ccount}) \times 100$$

Finally this percent of RGC will be correlated with results of blood test, where will be calculated the vitamins in plasma, trying to establish a model of vitamin dose and RGCs number that is associated with the disease progression.

2.1.6. GENERAL DESCRIPTION HPLC method

Tocopherol is the collective term for all methyl substituted tocols. The E-vitamins show pharmacological effects on the gonads (disturbance of fertility) and have influence on metabolism, on the muscles, the connective tissue and on the cell membrane because of the antioxidative property. At sufficient vitamin E levels the toxic effects of alcohol and heavy metals is reduced.

Vitamin E is extracted from the sample matrix in a short sample preparation. For this purpose, an aliquot of the plasma sample is transferred into a sample preparation vial (contains a lyophilized salt mixture) and is precipitated by addition of Precipitant P (contains an Internal Standard), subsequently. Afterwards the precipitate is separated by centrifugation and an aliquoted of the supernatant is mixed with Stabilizing Reagent S. Finally the sample is centrifuged and 50 µl of the supernatant is injected into the HPLC system. The sample clean-up procedure ensures highly purified sample extracts and thus allows a chromatography nearly without any additional peaks than those of the analytes and the internal standard.

A special reversed-phase column is used for the separation. The analytes are measured by a UV detector and, using the internal standard method, are quantitatively evaluated subsequent to calibration. The method is characterized by a very good linearity over a wide range of concentration. Easy sample preparation combined with selective detection enables reliable and reproducible results.

2.1.7. Data & Interpreting Analysis

Data will be reported as means and will be compared by One way ANOVA (analysis of variance) method followed by post hoc Tukey honestly significant difference (HSD) test using the software SPSS version 24 (Statistical Package for Social Science) with a 0.05 significance level. Additionally, paired-samples t-test will be conducted to determine whether the mean difference between paired observations is statistically significantly different from zero. Box plots will be used for detecting outliers in this analysis. In order to assess normality, Shapiro-Wilk test and Normal Q-Q Plots, will be applied.

The ANOVA / POST-HOC Tuckey variance analysis will be performed, with multiple comparisons between glaucoma groups and placebo in all the stages, Healthy, Early, Medium, Severe. Post-hoc tests will be conducted in order to confirm the differences between the groups. Post-hoc tests attempted to test the experimental error rate (usually alpha = 0.05) in the same way that the univariate ANOVA will be used instead of multiple t-tests. A paired-samples t-test will be conducted to determine whether the mean difference between, glaucoma patients and control group, after vitamin E 3, 6, and 9 months of use.

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