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Review

# Diet, Oxidative Stress, and Blood Serum Nutrients in Various Types of Glaucoma: A Systematic Review

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**Abstract:** Glaucoma is one of the most common causes of irreversible vision loss worldwide. It is an insidious disease with a multifactorial pathogenesis. Despite progress in treatment methods, prevention and lifestyle modifications may be useful in slowing the progression of this disease. This systematic review aimed to evaluate the influence of diet, oxidative stress, and disturbances in blood serum levels of nutrients on the incidence and severity of glaucoma based on scientific reports on the role of nutrition in the pathogenesis and course of glaucoma. This paper presents an analysis of the above issues; however, further research is required to develop this topic. Future clinical trials are needed to assess the influence of nutrition and to develop nutritional management strategies for patients with glaucoma.

**Keywords:** primary open angle glaucoma; primary angle-closure glaucoma; PEX glaucoma; diet; oxidative stress; nutrients serum level

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## 1. Introduction

Glaucoma is a multifactorial disease characterized by progressive neuropathy of the optic nerve. It affects approximately 70 million people worldwide, and its incidence is predicted to increase [1]. Changes in the morphology of the optic nerve disc leads to visual-field loss, progressive deterioration, and, finally, irreversible vision loss. Glaucomatous neuropathy is mainly caused by persistently high intraocular pressure (IOP); however, it is possible to develop glaucoma when the pressure is within the normal range (normal tension glaucoma [NTG]) [2].

Under normal conditions, the aqueous humor flows from the posterior chamber to the anterior chamber of the eye and is then drained through the outflow pathways: the trabecular meshwork (TM), the choroidal, and the iris. In primary open-angle glaucoma (POAG), outflow of the aqueous humor is impeded because of increased resistance at the levels of the above outflow pathways [3]. One of the most common causes of secondary OAG is pseudoexfoliation syndrome (PEX), characterized by the accumulation of fibrous deposits in the anterior segment of the eye, including the anterior chamber angle and lens capsule [4].

In angle-closure glaucoma (ACG), the peripheral part of the iris obscures the TM, which blocks the outflow of the aqueous humor [1]. In the course of glaucoma, morphological changes occur in many structures of the eye, including optic nerve fiber atrophy, apoptosis of retinal ganglion cells, excessive loss of the TM, and changes in the morphology of cells lining Schlemm's canal [1]. The main goal of pharmacological treatment is IOP lowering; however, it is associated with adverse events and may be inconvenient for the patient. Surgical methods that significantly improve glaucoma

control are constantly improving. Surgical treatment is directed at increasing the outflow of the aqueous humor using various methods, including trabeculectomy, canaloplasty, or the latest minimally invasive glaucoma surgery techniques [5]; although these are highly effective, they are not free from complications. Glaucoma is an insidious disease that develops asymptotically for an extended period of time, during which it is often unnoticed. The changes that occur during its course lead to irreversible vision loss, often impeding patients from engaging in professional activities and significantly altering everyday functioning [6]. It is therefore of paramount importance to investigate additional therapeutic methods to prevent and limit its course. There are scientific reports on the influence of nutrition and levels of selected nutrients on the risk of glaucoma or progression of the disease. The occurrence of oxidative stress in the body is important in the pathophysiology of glaucoma. Oxidative stress results from imbalance between the production of reactive oxygen species and the capacity of antioxidants and repair systems, leading to damage to lipids, proteins, and DNA structures, and subsequently to cellular destruction [7]. Deficiencies or over-supplementation of certain macro- and micronutrients also adversely affect the course of glaucomatous neuropathy. Given the multifactorial nature of glaucoma and its chronic course, the role of nutrition and appropriate choice of dietary nutrients should be considered as an adjunct to treatment or to inhibit disease progression.

The aim of this systematic review was to present an overview of the scientific literature on nutrients (vitamins, trace elements, and other antioxidants) that are known to have an impact on the development of different types of glaucoma and to determine the association of these nutrients with the course of the disease.

## **2. Nutrition, Blood Nutrient Levels of Oxidative Stress, and Glaucoma**

### *2.1 Primary Open-angle Glaucoma*

Oxidative stress plays a role in the pathogenesis of glaucoma, and the influence of dietary nutrients with antioxidant or pro-oxidant effects should be considered [5]. The effects of nutrition on the risk of OAG were evaluated in the prospective Rotterdam study with a population-based cohort of more than 3,500 participants. Consumption of specific nutrients was determined by questionnaires, and the participants were free of glaucoma at the time of the study. Participants diagnosed with glaucoma consumed a diet with a lower intake of antioxidant-rich foods, such as  $\beta$ -carotene, retinol, and B vitamins, i.e., B1 and B12, and a higher intake of magnesium- and vitamin E-rich foods than participants without glaucoma. The difference in the incidence was higher when dietary supplement users were excluded. These results may indicate the involvement of these components as factors that increase or decrease the risk of OAG [8].

Braakhuis et al studied the relationship between the use of various dietary products containing antioxidants and the occurrence of eye diseases related to oxidative stress, such as POAG, cataracts, or aged-related macular degeneration. The occurrence of these diseases was less frequent among participants with an increased dietary supply of fruits and vegetables rich in antioxidants, vitamin C, and  $\beta$ -carotene [9]. Other components whose dietary deficiencies may be associated with the occurrence of glaucoma are vitamin A and vegetable oils [9,10].

Both deficiencies and excessively high serum levels of particular nutrients often reflect disorders in the body. Markers of oxidative stress, as a cause of glaucoma development, and serum antioxidant or oxidant levels appear to be helpful in the diagnosis and study of disease progression.

The relationship between visual-field changes in patients with OAG and serum antioxidant and oxidant levels has been studied. Using the Diacron reactive oxygen metabolites, biological antioxidant potential (BAP), and sulfhydryl tests, markers of oxidative stress (lipid peroxides, iron-reducing activity, and thiol antioxidant activity) were evaluated using a free radical analyzer. A significant association was observed between decreased BAP values and significant visual-field loss in patients with POAG.

The weaker antioxidant capacity of the body may be associated with a more severe course of glaucoma, as reflected by the more extensive changes in the visual field. Additionally, the changes are more intense in POAG than in glaucoma with normal IOP [7].

Uric acid is a well-known antioxidant and a free-radical neutralizer in the body. It is a natural metabolite of purines, the main source of which is meat. The uric-acid level in the blood serum of patients with POAG was assessed and was observed that its level was significantly lower in patients than in controls. Additionally, the participants were divided into groups according to the progression of glaucomatous changes in the visual field (mean deviation), reflecting the stage of the disease. The lowest serum uric-acid levels were noted in patients in the group with the most severe disease course; however, when the patients were divided according to sex, a statistically significant relationship was observed in the male group [11].

Disturbed blood flow regulation affects optic nerve function. Nitric oxide (NO), a vasodilator, improves blood flow through the vessels, which may have a protective effect on the optic nerve. The effects of dietary NO on the development of POAG have been previously studied. High IOP was observed to be less frequent in participants consuming a diet rich in green leafy vegetables containing large amounts of nitrogen compounds, a source of NO [12].

The involvement of iron as one of the body's oxidants may be considered in the pathogenesis of glaucoma. According to studies, excessive dietary iron supply may correlate with an increased risk of glaucoma [10,13]. Moreover, a study by Lin et al. evaluated the relationship between the serum levels of ferritin, which is the body's iron store, and the occurrence of glaucoma. The prevalence of glaucoma was higher among participants with high ferritin levels, which may be related to the role of oxidative stress in the pathogenesis of glaucoma [14]. Additionally, a higher prevalence of glaucoma has been reported in individuals with increased calcium and iron supplementation [13].

## 2.2 Normal Tension Glaucoma

The effects of niacin (vitamin B3) deficiency and the development of glaucoma are considered to be independent of IOP. Decreased intake of products rich in vitamin B3 has been reported in individuals with glaucoma with pressure lower than 21 mmHg [15]. In addition to the influence of individual nutrients on the occurrence of glaucoma, the nutritional levels appear to modulate the risk of glaucoma. An association between reduced nutrient intake and low body mass index (<18.5 kg/m<sup>2</sup>) in women and an increased incidence of NTG in these individuals have been demonstrated [16].

Retinol belongs to the group of vitamin-A derivatives and has antioxidant function. The level of retinol in the blood serum of individuals with NTG was tested. The results were compared with those from participants with POAG and of a control group. Significantly lower levels of retinol in the serum of participants with NTG were observed compared to the control group and to participants with glaucoma with high IOP, which may indicate the influence of the retinol level on the occurrence and course of NTG [17].

Other compounds with a potential influence on the course of NTG are anthocyanins and *Ginkgo biloba* extract. These are known to improve blood circulation and have a protective and antioxidant effect on cells. The effects of anthocyanin therapy or *Ginkgo biloba* extract therapy and their influence on the improvement of vision parameters in individuals with NTG were analyzed. Improvement in visual acuity (logMAR best-corrected visual acuity) and visual-field parameters (Humphrey Visual Field test) was observed in connection with the administration of anthocyanins and improvement in visual-field parameters after *Ginkgo biloba* extract therapy. These results may suggest a positive influence of these compounds on the course of NTG [18].

## 2.3 Pseudoexfoliation Glaucoma

Some reports have suggested an effect of homocysteine on the deposition of PEX material and the occurrence of pseudoexfoliation glaucoma (PXG) [19]. Additionally,

consumption of dietary products with high folic acid folate content, which is known to lower homocysteine levels, reduces the risk of PXG [20].

Disturbances in the oxidative balance of the body have also been linked to the occurrence of glaucoma in the course of PXG. Serum samples were examined using spectrophotometric and enzymatic methods, and the total antioxidant status (TAS) was assessed in individuals with PEX glaucoma. Reduced levels of antioxidants were observed in the serum samples of patients compared to those of controls, which may indicate the involvement of oxidative stress in the pathogenesis of PXG [21].

Many trace elements affect cell and tissue functions. Reports have focused on the serum levels of trace metals and toxic elements in relation to glaucoma. Elevated levels of elements such as manganese (Mn), molybdenum (Mo), and mercury (Hg) have been observed in the serum of individuals with PXG, which may be related to the role of these elements in the pathogenesis of this condition [22].

#### 2.4 Angle-closure Glaucoma

Similar findings have been reported for ACG. In a study by Li et al., both TAS and superoxide dismutase levels were decreased, while the levels of oxidative compounds such as malondialdehyde (MDA) were increased in participants with advanced ACG with extensive visual-field loss, which may be a prognostic or pathogenetic factor in ACG [23].

Similar observations were reported by a study of patients with primary ACG regarding the uric-acid levels. In these patients, serum uric-acid levels were also lower than those in the control group, and the disease course was most severe in these patients [24].

### 3.3. Glaucoma and Vitamins

Supplementation with specific vitamins is recommended in the course of many diseases. The relationship between the intake of antioxidant vitamins A, C, and E, their serum levels, and the incidence of glaucoma was studied. No correlation was observed between the serum levels of vitamins A, E, and C and the occurrence of glaucoma. However, less frequent occurrence of glaucoma was found in participants who received supplementation with high doses of vitamin C [25].

In a study by Zanon-Moreno et al. the influence of the polymorphism of some genes related to vitamin C and E on the risk of POAG was investigated. A relationship between the rs1279683 polymorphism of the vitamin C cotransporter gene and the rs737723 polymorphism of the vitamin E-related protein gene and increased incidence of glaucoma was observed. Additionally, lower serum levels of vitamin C and E were noted in individuals with glaucoma [26].

Similar results have been reported for vitamin D in its form 25 (OH). Neither low nor high serum levels of this vitamin are associated with changes in IOP. Additionally, in individuals with low serum vitamin D levels, no changes in IOP were observed after supplementation with 20000 IU of vitamin D twice weekly [27]. Moreover, in a study by Kim et al. glaucomatous changes were observed more often in women with low vitamin D 25 (OH) serum levels [28].

In another study, the serum level of vitamin 25 (OH) D3 was determined, and the relationship between the polymorphism of some genes encoding vitamin D3 receptors and the occurrence of POAG was investigated. A lower serum level of vitamin D3 was found in participants with POAG. Additionally, the presence of the vitamin D3 receptor BsmI and TaqI genotypes was associated with a higher incidence of POAG [29].

As mentioned earlier, the relationship between homocysteine levels and the occurrence of PEX glaucoma is known, as is the protective effect of folate (vitamin B11). The relationship between serum levels of B vitamins, i.e., vitamins B6, B12, and folate, and the level of homocysteine in various types of glaucoma (POAG, PXG, and NTG) was investigated. A high level of vitamin B6 in NTG and POAG was observed compared with the control groups and an increased level of homocysteine in PXG, but no statistically significant differences between the level of homocysteine and other types of glaucoma were

shown [30]. Similarly, in a study by Kang et al. the effects of dietary supplementation with B vitamins B6, B11 (folic acid), and B12 were studied. No association was found between the occurrence of PXG and diets rich in vitamins B6 and B12 [20].

#### 4. Discussion

The information contained in our analysis strongly indicates that there is a connection between diet and disturbances in the levels of selected blood serum elements and the occurrence of different types of glaucoma. These factors may also influence disease progression. The influence of oxidative stress and the antioxidant capacity of the body on the occurrence of glaucoma is particularly marked. In a study by Mousa et al, TAS was evaluated in serum samples from patients with POAG, ACG, and PXG. The involvement of oxidative stress in the pathogenesis of glaucoma is supported by the fact that reduced serum TAS levels were found in all aforementioned types of glaucoma [31].

In addition, reduced antioxidant levels can be considered when assessing the severity of the course of POAG, as indicated by a study by Abu-Amero et al [32]. Moreover disorders in the oxidative balance, which includes increased levels of selected oxidants occur in PEX and consequently in PXG. Under these conditions, increased levels of MDA, which is involved in lipid oxidation, were observed. Simultaneously, the levels of antioxidant enzymes decrease [33].

The results of the analyzed studies suggest a protective effect of a diet rich in antioxidants and oxidative imbalance as a possible pathogenetic factor in different types of glaucoma. However, our study had some limitations. The studies included in the analysis differed in terms of inclusion criteria and number of participants. In addition, the definition of glaucoma was not precisely specified in some articles, which could have affected the results, especially concerning the division into different types of glaucoma. Some studies included questionnaires in the methodology that were completed subjectively by the participants, which could have led to discrepancies in the results obtained. A meta-analysis that considers the division into glaucoma types, assessment of the body's oxidative balance, and evaluation of the diet and eating habits of the participants included in the study is needed to explore the topic more thoroughly.

Further, our study did not consider other aspects relating to the onset of glaucoma. Indeed, many etiological factors are involved in the pathophysiology of this disease. In addition to genetic causes, environmental influences, such as pesticide exposure, lifestyle, and dietary patterns, also play a role. Finally, insufficient intake of dietary products rich in omega-3 fatty acids, such as fish, and heavy smoking may increase the risk of POAG [34].

#### 5. Conclusions

Existing reports allow for a better understanding of the multifactorial etiology of glaucoma and the pathophysiological mechanisms involved in its development. Increasing the knowledge on diet, oxidative balance, and appropriate levels of particular nutrients in the blood serum may prove helpful in monitoring or diagnosing glaucoma or constitute an element of supplementary treatment for this disease. There are promising findings on the influence of certain groups of nutrients; however, their clinical validation is difficult because their administration should be applied for the entire duration of a patient's life. Studies with longer follow ups and larger sample sizes are required to increase our understanding of the role of nutrition in glaucoma.

#### 6. Method of Literature Search

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PubMed database was used for the literature search for articles published between November 2011 and November 2021. The terms "Glaucoma and nutrition," "Glaucoma and nutrients," "nutrients serum level in

glaucoma," "trace elements and glaucoma," "diet and glaucoma," "pseudoexfoliation glaucoma and diet," and "angle-closure and diet" were used.

Articles inconsistent with the topic and abstracts available only as conference papers were excluded. Full-text publications were selected based on the compatibility of abstracts with the topic of the study. Additionally, the literature included in the selected articles was also reviewed to locate articles not found in the original searches.

We included prospective randomized control trials, case-control studies, cross-sectional studies, and publications with patients with a diagnosis of POAG, ACG, or PXG. Review articles and case reports were excluded.

### 6.1. Risk of Bias Assessment

The methodological quality of the included studies was evaluated independently by two authors (J.K. and M.M.).

### 6.2. Data Extraction

The demographics, participant characteristics, interventions used, and outcomes used for the purpose of this study were reviewed by the authors, and disagreements were resolved through discussion. A PRISMA schematic is shown in Figure 1. Overall, 394 publications were analyzed for diet, oxidative stress, and serum levels of selected elements in relation to the incidence of POAG, primary closed-angle glaucoma, and PEX glaucoma. From the retrieved articles, titles and abstracts were skimmed, and a thorough evaluation of the full text of suitable studies was performed. After removing duplicates, review articles, case reports, and off-topic publications, and after including publications selected during the literature review, 34 articles were included. These publications described diet and nutrient intake (Table 1) and changes in the serum levels of selected elements, markers of oxidative stress, and their association with glaucoma (Table 2). The remaining publications approximated the subject matter of the above analysis. In addition, the reference lists of all identified studies were reviewed and searched.

**Table 1.** Selected diet component intake and risk of glaucoma occurrence.

Reference	Event	Risk of glaucoma occurrence
[8]	Low antioxidant intake	-
[9]	High antioxidant intake	-
[10]	Low vitamin A and vegetable oil intake	-
[10,13]	High iron intake	-
[15]	Low vitamin B3 intake	-
[16]	Low BMI in women	-
[12]	High green leave (source of NO) intake	-
[20]	High vitamin B11 (folic acid) intake	-
[34]	Low omega-3 fat intake	-
[18]	Anthocyanin and <i>Gingko biloba</i> extract administration	No mention, but improvement of visual function

BMI, body mass index; NO, nitric oxide

**Table 2.** Serum elements and oxidative stress in glaucoma.

Reference	Event	Observation	Risk of glaucoma occurrence
[7]	Low BAP	Defects in the visual field	-
[19]	High homocysteine level	PEX material deposition	-
[21]	Low TAS	PEX material deposition	-
[23]	Low TAS	Higher risk of angle-closure glaucoma	-
[14]	High serum ferritin level	Increased iron resources	-
[11]	Low serum uric-acid level	Defects in the visual field	-
[24]	Low serum uric-acid level	Higher risk of angle-closure glaucoma	-
[25]	Serum vitamin A, E, and C levels	No observation	No impact
[27]	Serum vitamin D 25 (OH) level	No observation	No impact
[22]	Higher serum levels of molybdenum, manganese, and mercury	PEX material deposition	-
[33]	Higher level of MDA	Higher oxidant level	-
[17]	Lower level of retinol	Higher risk of NTG	-
[26]	Polymorphism in vitamins C and E	Lower level of vitamin C	-
[28]	Lower vitamin D 25(OH) level	Glaucomatous changes	-
[29]	Polymorphism in vitamin D3	Lower level of vitamin D	-
[30]	NTG and POAG occurrence	Higher level of vitamin B6	-

BAP, biological antioxidant potential; MDA, malondialdehyde; NTG, normal tension glaucoma; POAG, primary open-angle glaucoma; PEX, pseudoexfoliation syndrome; TAS, total antioxidant status

**Figure 1.** Flowchart showing the proposed approach.

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