Review Article

The Association of Oxidative Stress Status with Open-Angle Glaucoma and Exfoliation Glaucoma: A Systematic Review and Meta-Analysis

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Purpose. To systematically evaluate the associations between oxidative stress status and different types of glaucoma. Design. Systematic review and meta-analysis. Methods. We searched PubMed, EMBASE, and the Web of Science for randomized controlled trials written in the English language between January 1, 1990, and November 30, 2016. A random effects model was used to estimate oxidative stress status along with weighted mean differences and 95% confidence intervals (CIs). A funnel plot analysis and Egger’s test were performed to assess potential publication bias. Main outcome measures. Oxidative stress status was abnormal and different in patients with OAG (open-angle glaucoma) and EXG (exfoliation glaucoma). Results. Blood TAS (total antioxidant status) was lower in the OAG group than in the control group, with a mean difference of 0.580 mmol/L (p < 0.0001, 95% CI = −0.668 to −0.492). The aqueous humor SOD (superoxide dismutase), GPX (glutathione peroxidase), and CAT (catalase) levels were higher in the OAG group than in the control group, with mean differences of 17.989 U/mL (p < 0.0001, 95% CI = 14.579–21.298), 12.441 U/mL (p < 0.0001, 95% CI = 10.423–14.459), and 1.229 fmol/mL (p = 0.042, 95% CI = 0.043–2.414), respectively. Blood TAS was lower in the EXG group than in the control group, with a mean difference of 0.262 mmol/L (p < 0.0001, 95% CI = −0.393 to −0.132). However, there were no differences in blood TOS and aqueous humor TOS between the EXG group and the control group. Conclusions. This meta-analysis indicates that OAG patients had a lower TAS in the blood and higher levels of SOD, GPX, and CAT in the aqueous humor, while EXG patients only had a decreased TAS in the blood.

1. Introduction

Glaucoma represents a group of diseases defined by characteristic visual dysfunction and optic neuropathy and is a major cause of irreversible blindness worldwide [1]. It has been estimated that the number of people (aged 40–80 years) with glaucoma all over the world was 64.3 million in 2013, increasing to 76.0 million in 2020 and 111.8 million in 2040 [2]. Because of the rapid increase in aging populations worldwide, the prevalence of glaucoma also increased year by year.

The pathologic mechanisms leading to glaucoma are still unclear. Although high intraocular pressure is considered to be the most important risk factor for glaucoma [3], other concomitant factors may also play important roles in the etiology and pathology of the disease, including high glutamate levels [4], alterations in nutritional status [5], vascular factors [6–8], dysfunction of the immune system [9–11], and oxidative stress [12–14]. Growing evidence obtained from clinical and experimental studies over the past decade strongly suggested the involvement of oxidative stress in the degeneration of retinal ganglion cells (RGCs) in
glaucoma [14, 15]. Oxidative stress may damage the structure of the trabecular meshwork and increase the resistance to aqueous humor outflow, thus causing the retina to be exposed to ocular hypertension and neurological damage [16]. Progressive neurological damage is followed by RGC death and axon atrophy, which finally lead to irreversible vision loss [17, 18]. Oxidative stress reflects a disbalance between pro-oxidants and antioxidants [19]. In normal conditions, the generation of damaging reactive oxygen species (ROS) is blocked by an antioxidant defense, such as SOD (superoxide dismutase), GPX (glutathione peroxidase), and CAT (catalase). It has been postulated that, in glaucoma, the existence of excess ROS cannot be eliminated by antioxidants effectively. Thus, ROS may damage ocular tissues and produce many small molecules that can be detected both in serum and the aqueous humor. Although the evaluation of general markers of oxidative stress in different types of glaucoma has been assessed in various studies [12, 15, 19, 20], the results are under debate and the study samples were all relatively small. Therefore, we conducted a systematic review and meta-analysis to evaluate oxidative stress status in different types of glaucoma and further investigate the association between oxidative stress and glaucoma.

2. Methods

2.1. Search Methods. Studies were aggregated from three databases, including PubMed, the Web of Science, and EMBASE. Specifically, randomized controlled trials (RCTs) written in the English language from January 1, 1990, through November 30, 2016, were selected. The following search terms were used to retrieve relevant studies: (glaucoma (Title/Abstract)) AND (total antioxidant (Title/Abstract) OR total oxidant (Title/Abstract) OR malondialdehyde (Title/Abstract) OR superoxide dismutase (Title/Abstract) OR glutathione peroxidase (Title/Abstract) OR catalase (Title/Abstract)). Moreover, a manual search was performed by checking the reference lists of the clinical trials, meta-analyses, and systematic reviews that were examined. Two reviewers (Shengjie Li and Binghua Tang) completed the literature search independently.

2.2. Inclusion Criteria. We included studies that met all of the following criteria in the meta-analysis:

1. The investigation involved random sampling or cluster sampling
2. The outcome was suitable for a meta-analysis when subjects and control subjects were measured
3. Cataract subjects/healthy subjects served as the control group
4. The papers were published in the English language
5. It was possible to obtain the full article

A flow chart illustrating the article search process is presented in Figure 1.

2.3. Data Extraction. We extracted the following data from each study: (1) the name of the first author, (2) the country/region of the study area, (3) the year in which the study was conducted, (4) the age range/mean age of the subjects, (5) the sample size of the study, (6) the method used to sample subjects, (8) the criteria used to diagnose glaucoma, and (9) the required outcome measures. We conducted a focused discussion to resolve any disagreements.

2.4. Quality Assessment. The quality assessments of the studies were based on previously reported examination guidelines for glaucoma studies [21, 22]. Five key criteria were used by the two independent investigators to estimate study quality: (1) the sampling scheme, (2) the description of the study population characteristics was adequate, (3) a clear data description was provided, (4) diagnostic criteria for different types of glaucoma, and (5) the detection method of oxidative stress parameters. For each item, studies that were “clear or adequate” scored one point, whereas a “no” scored zero points. A study was considered to be of adequate quality if the quality score was greater than or equal to three. Studies of an inadequate quality were excluded from this meta-analysis.

2.5. Statistical Analysis. The statistical analyses were performed using Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood Cliffs, NJ, USA; http://www.meta-analysis.com). The heterogeneity of the pooled studies was estimated using the χ²-based Q statistic and I² metric. If heterogeneity was observed, a random-effects model was used; otherwise, a fixed-effects model was applied. We conducted direct comparisons using a random-effects model to estimate weighted mean differences and 95% confidence intervals (CIs). A sensitivity analysis, funnel plot analysis, and Egger’s test were performed to assess potential publication bias. A value of p < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the Studies. A flow chart illustrating the article search process is presented in Figure 1. Using the initial search strategy, we identified 482 articles, and 460 articles were excluded. A total of 22 studies [19, 23–43] were included in this meta-analysis. Detailed characteristics of each included study are presented in Tables 1–4. Twenty-two studies were categorized into four groups according to the type of glaucoma. Specifically, 4 studies were classified in an angle-closure glaucoma (ACG) group, 11 studies in an open-angle glaucoma (OAG) group, 2 studies in a normal tension glaucoma (NTG) group, and 17 studies in an exfoliation glaucoma (EXG) group. Some studies examined multiple types of glaucoma and were placed in multiple groups, which is why more than 22 studies are listed above.
The different sources of specimens (blood or aqueous humor) and the oxidative stress parameters of the studies are as follows:

1. In the 4 studies from the ACG group, 3 sampled blood (total antioxidant status (TAS) 2, MDA 1) and 1 sampled aqueous humor (SOD 1, GPX 1, CAT 1).
2. In the 11 studies from the OAG group, 5 sampled blood (TAS 3, total oxidant status (TOS) 1, MDA 2, SOD 2, CAT 1) and 6 sampled aqueous humors (TAS 3, TOS 1, MDA 2, SOD 4, GPX 4, CAT 4).
3. In the 2 studies from the NTG group, both sampled blood (TAS 2, TOS 1).
4. In the 17 studies from the EXG group, 10 sampled blood (TAS 7, TOS 4, MDA 2, SOD 1, CAT 3) and 7 sampled aqueous humors (TAS 4, TOS 3, SOD 1, GPX 1, CAT 3).

We performed a meta-analysis if the studies examining the same type of glaucoma, the same type of oxidative stress parameters, and the same type of specimens scored greater than or equal to three in our quality assessment. In brief, eight subgroup meta-analyses were performed in this study. The quality of the included trials is shown in Table 5.

3.2. Meta-Analysis of the Association of Oxidative Stress Status with OAG. Detailed characteristics of studies in the OAG group are presented in Table 2. The blood TAS was lower in the OAG group than in the control group, with a mean difference of 0.580 mmol/L ($p < 0.0001$, 95% CI = −0.668 to −0.492); however, there was significant heterogeneity across the three studies ($I^2 = 68.725\%$, $p = 0.041$; Figure 2). The aqueous humor SOD levels were higher in the OAG group than in the control group, with a mean difference of 17.989 U/mL ($p < 0.0001$, 95% CI = 14.579–21.298), but, again, there was significant heterogeneity across the four studies ($I^2 = 91.747\%$, $p < 0.0001$; Figure 3). The aqueous humor GPX levels were higher in the OAG group than in the control group, with a mean difference of 12.441 U/mL ($p < 0.0001$, 95% CI = 10.423–14.459), and there was also significant heterogeneity across the four studies ($I^2 = 90.855\%$, $p < 0.0001$; Figure 4). The aqueous humor CAT levels were higher in the OAG group than in the control group, with a mean difference of 1.229 fmol/mL ($p = 0.042$, 95% CI = 0.043–2.414). There was no significant heterogeneity across the four studies ($I^2 = 59.660\%$, $p = 0.059$; Figure 5).

3.3. Meta-Analysis of the Association between Oxidative Stress Status and EXG. Detailed characteristics of the studies in the
Table 1: The level of oxidative stress status with ACG.

| First author | Year  | Country     | ACG group | Control group |
|--------------|-------|-------------|-----------|---------------|
| Ahmed Mousa  | 2015  | Saudi Arabia| 139       | 191           |
| Khaled K. Abu-Amero | 2014 | Saudi Arabia| 139       | 191           |
| Dong Chang   | 2011  | China       | 50        | 60            |
| Amita Goyal  | 2014  | India       | 30        | 40            |

ACG: angle-closure glaucoma; MDA: malondialdehyde; SOD: superoxide dismutase; GPX: glutathione peroxidase.
| First author                  | Year | Country          | N  | Age (years) | Total antioxidant status | Total oxidant status | OAG group | Control group | MDA     | SOD     | GPX     | Catalase | MDA     | SOD     | GPX     | Catalase |
|------------------------------|------|------------------|----|-------------|--------------------------|----------------------|------------|---------------|---------|---------|---------|----------|---------|---------|---------|----------|
| Blood                        | 2016 | Turkey           | 53 | 58.81 ± 12.23 | 1.046 ± 0.84 (μmol/L)    | 0.47 ± 0.179          | 52         | 61.53 ± 10.95 | 0.47 ± 0.179 | 1.1 ± 0.22 (mmol/L) | 0.97 ± 0.43 (mmol/L) | 1.95 ± 0.76 (μmol/L) | 56.29 ± 2.201 (μmol/L) |
| Ugur Yılmaz Mumcu            | 2016 | Turkey           | 53 | 58.81 ± 12.23 | 1.046 ± 0.84 (μmol/L)    | 0.47 ± 0.179          | 52         | 61.53 ± 10.95 | 0.47 ± 0.179 | 1.1 ± 0.22 (mmol/L) | 0.97 ± 0.43 (mmol/L) | 1.95 ± 0.76 (μmol/L) | 56.29 ± 2.201 (μmol/L) |
| Ahmed Mousa                 | 2015 | Saudi Arabia     | 147 | 66.8 ± 17.9   | 0.47 ± 0.32 (mmol/L)     | 0.47 ± 0.32 (mmol/L)  | 148        | 61.1 ± 10.8   | 0.47 ± 0.32 (mmol/L) | 0.47 ± 0.32 (mmol/L)  | 0.47 ± 0.32 (mmol/L)  | 0.47 ± 0.32 (mmol/L)  | 0.47 ± 0.32 (mmol/L)  |
| Khaled K. Abu-Amrero        | 2013 | Saudi Arabia     | 139 | 62.3 ± 11.5   | 0.47 ± 0.32 (mmol/L)     | 0.47 ± 0.32 (mmol/L)  | 148        | 61.1 ± 10.8   | 0.47 ± 0.32 (mmol/L) | 0.47 ± 0.32 (mmol/L)  | 0.47 ± 0.32 (mmol/L)  | 0.47 ± 0.32 (mmol/L)  | 0.47 ± 0.32 (mmol/L)  |
| O. Awodelo                  | 2015 | Nigeria          | 40  | 57.7 ± 112    | 0.6 ± 0.1 mmol/L         | 0.6 ± 0.1 mmol/L      | 19.6 ± 2.6  | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    |
| Mesut Erdurmuş             | 2011 | Turkey           | 23  | 62.3 ± 90     | 0.6 ± 0.1 mmol/L         | 0.6 ± 0.1 mmol/L      | 19.6 ± 2.6  | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    |
| Mesut Erdurmuş              | 2011 | Turkey           | 23  | 62.3 ± 90     | 0.6 ± 0.1 mmol/L         | 0.6 ± 0.1 mmol/L      | 19.6 ± 2.6  | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    |
| Aqueous humor               | 2011 | Turkey           | 23  | 62.3 ± 90     | 0.6 ± 0.1 mmol/L         | 0.6 ± 0.1 mmol/L      | 19.6 ± 2.6  | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    | 19.6 ± 2.6   | 19.6 ± 2.6    |
| Esra Ergan                  | 2016 | Turkey           | 15  | 67.1 ± 9.6    | 2.95 ± 2.0 mmol/L        | 2.95 ± 2.0 mmol/L     | 31.59 ± 12.7| 31.59 ± 12.7 | 31.59 ± 12.7 | 31.59 ± 12.7 | 31.59 ± 12.7 | 31.59 ± 12.7 | 31.59 ± 12.7 | 31.59 ± 12.7 |
| Asaad A. Ghanem            | 2010 | Egypt            | 30  | 54.5 ± 4.98   | 0.48 ± 0.1 μmol/L        | 0.48 ± 0.1 μmol/L     | 39.97 ± 2.48| 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 |
| S.M. Ferreira               | 2009 | Argentina        | 25  | 70 ± 10       | 0.48 ± 0.1 μmol/L        | 0.48 ± 0.1 μmol/L     | 39.97 ± 2.48| 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 |
| Vicente Zanon Moreno        | 2008 | Spain            | 50  | 70.92 ± 8.19  | 0.48 ± 0.1 μmol/L        | 0.48 ± 0.1 μmol/L     | 39.97 ± 2.48| 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 | 39.97 ± 2.48 |
| Sandra M. Ferreira          | 2005 | Argentina        | 24  | 71 ± 2        | 52 ± 7 umol/l Trolox     | 52 ± 7 umol/l Trolox  | 41.7 ± 2.7  | 41.7 ± 2.7    | 41.7 ± 2.7   | 41.7 ± 2.7    | 41.7 ± 2.7   | 41.7 ± 2.7    | 41.7 ± 2.7   | 41.7 ± 2.7    |
| Armita Goyal                | 2004 | India            | 30  | 46.19 ± 6.79  | 41.7 ± 2.7 U/ml          | 41.7 ± 2.7 U/ml       | 21.70 ± 4.93| 21.70 ± 4.93 | 21.70 ± 4.93 | 21.70 ± 4.93 | 21.70 ± 4.93 | 21.70 ± 4.93 | 21.70 ± 4.93 | 21.70 ± 4.93 |

OAG: open-angle glaucoma; MDA: malondialdehyde; SOD: superoxide dismutase; GPX: glutathione peroxidase.
EXG group are presented in Table 4. Blood TAS was lower in the EXG group than in the control group, with a mean difference of 0.262 mmol/L ($p < 0.0001$, 95% CI = −0.393 to 0.132). The seven studies were, however, significantly heterogeneous ($I^2 = 90.579\%$, $p < 0.0001$; Figure 6). There was no difference in blood TOS between the EXG group and the control group ($p = 0.563$, 95% CI = −60.657–3.017; Figure 7). There was also no difference in the aqueous humor TAS between the EXG group and the control group ($p = 0.588$, 95% CI = −0.540–0.306; Figure 8) or in the aqueous humor TOS between the EXG group and the control group ($p = 0.135$, 95% CI = −1.979–14.695; Figure 9).

### 3.4. Sensitivity Analysis and Publication Bias

In the meta-analysis of the association between aqueous humor CAT levels and OAG, a sensitivity analysis revealed that three studies influenced the result. Three studies influenced the meta-analysis results regarding the association between blood TOS and EXG, four studies influenced the results regarding the association between aqueous humor TAS and EXG, and two studies influenced the meta-analysis results regarding the association between aqueous humor TOS and EXG (Table 6). A funnel plot analysis and Egger’s test suggested that no publication bias existed in the subgroup analysis (both $p > 0.05$; Supplementary Figures 1–8) except in the blood TAS of the EXG subgroup ($p = 0.015$; Supplementary Figure 6).

### 4. Discussion

The pathological mechanisms of OAG and EXG are significantly different, which indicates the specific pathogeneses may also be different. Although oxidative stress is involved in both OAG and EXG, whether it is involved in different types of glaucoma remained to be investigated. In this work, we assessed all studies reporting the level of oxidative and antioxidative markers in aqueous humor or serum samples of glaucoma patients and found that the blood TAS was lower in the OAG group than in the control group, but antioxidative enzymes, including SOD, GPX, and CAT, were increased in the aqueous humors of the OAG group. At the same time, we also found that blood TOS was lower in the EXG group than in the control group, but there was no difference between the blood TOS and the aqueous humor TAS and TOS in the EXG group.

OAG is a multifactorial disease in which aging, genetic factors, inflammation, and oxidative stress may play a specific role [15, 36, 44]. An increased intraocular pressure is a high risk factor of POAG, but normal intraocular pressure can also lead to optic nerve damage and loss of vision in POAG [45]. Although the causes of OAG are unknown, oxidative stress appears to play a role in progressive glaucomatous optic nerve damage [23, 30, 36]. The blood TAS in the meta-analysis of OAG patients decreased, which suggested a breakdown of the balance between the ROS generation and clearance systems. It has been reported that RGCs probably die through an apoptotic process, ultimately leading to glaucomatous optic neuropathy [46, 47], and apoptotic processes are known to involve oxidative stress [48]. Therefore, we speculated that the degeneration of RGCs was induced by oxidative stress. In this meta-analysis, we also found that the activity of SOD, GPX, and CAT in the aqueous humors of OAG patients increased. All of those enzymes have antioxidant effects despite having different specific functions. SOD catalyzes the oxidation/reduction conversion of superoxide radicals to molecular oxygen and hydrogen peroxide [49]. CAT is another key antioxidant enzyme that protects against harmful peroxide by converting hydrogen peroxide to water and oxygen, thereby mitigating its toxic effects [49]. GPX catalyzes the reduction of hydrogen peroxide by two molecules of glutathione as part of an ROS defense system [49]. Therefore, we speculated that the antioxidant enzyme levels increased as a means of resisting the excess ROS in the aqueous humor to avoid their damage to the trabecular meshwork or RGCs. However, there was significant heterogeneity across the studies included in our meta-analysis. The reasons may be that the study population was different, and despite the fact that the same methods were used to detect indicators, the regents or procedures were different.

EXG is an age-related disorder characterized by abnormal synthesis and deposition of extracellular fibrillar material and is the most common cause of secondary OAG [50]. Although the precise mechanisms underlying the development of exfoliative syndrome and the subsequent progression from exfoliative syndrome to EXG remain unclear, a number of studies in the last decade suggest that increased oxidative stress, which leads to exfoliation-induced tissue damage and pathological alterations of the extracellular matrix, is involved in the pathobiology of EXG.
### Table 4: The level of oxidative stress status with EXG.

| First author   | Year | Country | Age (years) | EXG group | Control group |
|----------------|------|---------|-------------|-----------|---------------|
| Blood          |      |         |             | N         | Age (years)   |
| Feyza Dursun   | 2015 | Turkey  | 26          | 66.19 ± 6.88 | 67.03 ± 6.34 |
| Ahmed Mousa    | 2015 | Saudi Arabia | 54        | 67.6 ± 10.4 | 61.8 ± 11.7 |
| Khaled K. Abu-Amero | 2011 | Saudi Arabia | 54    | 67.57 ± 10.43 | 67.72 ± 10.60 |
| Mesut Erdurmuş | 2011 | Turkey  | 24          | 65.7 ± 8.0 | 57.4 ± 5.6 |
| George G. Koliasco | 2008 | Greece | 20          | 70.9 ± 7.9 | 70.8 ± 7.7 |
| George G. Koliasco | 2009 | Greece | 20          | 71.0 ± 7.5 | 70.8 ± 7.7 |
| Birsen Can Demirdögen | 2014 | Turkey | 32          | 70 (67.0–76.0) | 70.5 (62.3–78.3) |
| Birsen Can Demirdögen | 2014 | Turkey | 30          | 72 (64.5–77.8) | 70.5 (62.3–78.3) |
| Mehmet Tektikoglu | 2016 | Turkey | 34          | 65.53 ± 9.1 | 62.34 ± 7.7 |
| Rana Sorkhabi   | 2011 | Iran    | 27          | 63.89 ± 7.37 | 65.22 ± 9.79 |
| Koliakos       | 2009 | Greece  | 20          | 70.9 ± 7.9 | 70.8 ± 7.7 |
| Rana Sorkhabi   | 2011 | Iran    | 27          | 63.89 ± 7.37 | 65.22 ± 9.79 |
| Estrin Ergan   | 2016 | Turkey  | 15          | 67.1 ± 9.6 | 67.0 ± 9.8 |
| Feyza Dursun   | 2015 | Turkey  | 26          | 67.34 ± 6.93 | 67.03 ± 6.34 |
| Emrullah Beyazdiz | 2014 | Turkey | 17          | 69.8 ± 8.6 | 68.9 ± 12.0 |
| S.M. Ferreira   | 2009 | Argentina | 25        | 73 ± 2    | 27 ± 3 (U/ml) |
| George G. Koliasco | 2008 | Greece | 20          | 70.9 ± 7.9 | 70.8 ± 7.7 |
| George G. Koliasco | 2009 | Greece | 20          | 71.0 ± 7.5 | 70.8 ± 7.7 |
| Rana Sorkhabi   | 2011 | Iran    | 27          | 63.89 ± 7.37 | 65.22 ± 9.79 |

EXG: exfoliative glaucoma; MDA: malondialdehyde; SOD: superoxide dismutase; GPX: glutathione peroxidase.
| Name                   | Sampling scheme                  | Population characteristics | Data description | Diagnostic criteria | Methods                  | Score |
|------------------------|----------------------------------|----------------------------|------------------|---------------------|--------------------------|-------|
| Ugur Yilmaz Mumcu      | Random stratified sample         | Adequate Clear             | Clear 1          | HPLC                |                          | 5     |
| Esra Ergan             | Random stratified sample         | Adequate Clear             | Clear 2          | Clear 3             | Colorimetric method      | 5     |
| Necat Yilmaz           | Random stratified sample         | Adequate Clear             | Clear 4          | Clear 5             | Colorimetric measurement method | 5     |
| Feyza Dursun           | Random stratified sample         | Adequate Clear             | No               | Colorimetric method |                          | 4     |
| Ahmed Mousa            | Random stratified sample         | Adequate Clear             | Clear 6          | Colorimetric method |                          | 5     |
| Emrullah Beyaziyildiz  | Random stratified sample         | Adequate Clear             | Clear 7          | Colorimetric-based assay |                      | 5     |
| Khaled K. Abu-Amero    | Random stratified sample         | Adequate Clear             | Clear 8          | Spectrophotometric method |                      | 4     |
| O. Awodelo             | Random stratified sample         | Adequate Clear             | Clear 9          | Thiobarbituric acid-reacting substance (TBARS) production |                      | 5     |
| Dong Chang             | Random stratified sample         | Adequate Clear             | Clear 10         | Colorimetric-based assay |                      | 5     |
| Khaled K. Abu-Amero    | Random stratified sample         | Adequate Clear             | Clear 11         |                      |                          | 5     |
| Kenya Yuki             | Random stratified sample         | Adequate Clear             | Clear 12         | Colorimetric method |                          | 5     |
| Asaad A. Ghanem        | Random stratified sample         | Adequate Clear             | Clear 13         | Thiobarbituric acid reaction/ spectrophotometry |                      | 5     |
| S.M. Ferreira          | Random stratified sample         | Adequate Clear             | Clear 14         | Spectrophotometrically |                      | 5     |
| George G. Koliakos     | Random stratified sample         | Adequate Clear             | Clear 15         |                      |                          | 4     |
| Vicente Zanon Moreno   | Random stratified sample         | Adequate Clear             | No               | Colorimetric technique |                      | 4     |
| S.M. Ferreira          | Random stratified sample         | Adequate Clear             | Clear 16         | Chemiluminescence/ spectrophotometrically |                      | 5     |
| Birsen Can Demirdögen  | Random stratified sample         | Adequate Clear             | Clear 17         | Colorimetric method |                          | 5     |
Patients >45 years old were diagnosed with PEG if they showed typical pseudoexfoliation material (PEM) on the lens and/or papillary border with an IOP ≥22 mmHg, cup-to-disc ratio ≥0.3, generalized or partial rim notching on the optic nerve head, peripapillary choroidal atrophy or splinter hemorrhage, and glaucomatous visual field damage according to the Advanced Glaucoma Intervention Study criteria. Patients with all of these findings, except PEM, were diagnosed with POAG. (3) Patients >45 years old were diagnosed with PEG if they showed typical pseudoexfoliation material (PEM) on the lens and/or papillary border with an IOP ≥22 mmHg, cup-to-disc ratio ≥0.3, generalized or partial rim notching on the optic nerve head, peripapillary choroidal atrophy or splinter hemorrhage, and glaucomatous visual field damage according to the Advanced Glaucoma Intervention Study criteria. Patients with all of these findings, except PEM, were diagnosed with POAG. (4) Patients with an IOP of 21 mmHg or lower, displaying glaucomatous changes in the optic disc (atrophy, neuroretinal rim loss, and peripapillary hemorrhage) and in the visual field were diagnosed as having NTG. (5) A diagnosis of PEXG was given if the results for the anterior segment of the pseudoexfoliative component showed an IOP exceeding 21 mmHg without typical optic nerve head changes or visual field effects. (6) At least three of the following: (i) clinical documentation of angle closure, defined as the presence of appositional or synnechial closure of the anterior chamber angle involving at least 270° by gonioscopy in either eye; (ii) intraocular pressure elevated to a level ≥21 mmHg measured by Goldmann applanation tonometry; (iii) evidence of characteristic glaucomatous optic disk damage with excavation of the disc causing a cup-to-disc ratio (c/d) vertically of at least 0.70 in at least one eye; and (iv) characteristic peripheral visual field loss including nerve fiber bundle defects (nasal step, arcuate scotoma, and generalized depression) in the absence of other causes or explanation; (iii) age greater than 40 years at the time of recruitment, and (iv) open anterior chamber angles bilaterally on gonioscopy. (8) The diagnostic criteria for PACG were as follows: open and non-occludable anterior chamber angles with gonioscopy (Volk 3 Mirror Gonio Lens, Mentor, USA), glaucomatous optic disc cupping was identified as a vertical cup-to-disc ratio of optic nerve head 0.6 or more, difference of the vertical cup-to-disc ratio 0.2 or more between both eyes, rim width at superior portion (11–1 h) or inferior portion (5–7h) of 0.2 or less of disc diameter, or the presence of nerve fiber layer defect. (9) Subjects with PEG were defined as those with clinical evidence of exfoliation material on the pupil margin or anterior lens surface, the presence of glaucomatous optic neuropathy with associated visual field loss in one or both eyes, and documented IOP ≥22 mmHg in either eye. (10) POAG was defined as a progressive optic neuropathy characterized by specific glaucomatous optic nerve head damage and visual field loss associated with elevated IOP. (11) A presence of PEX in PEG is confirmed clinically by small, white deposits of material in the anterior segment, most commonly on the pupillary margin or anterior lens surface. (12) After the diagnosis of primary open-angle glaucoma was made, each patient’s IOP was measured at seven time-points over 24 hr (i.e., at 6, 9, 12, 15, 18, 21, and 24 o’clock) with Goldmann applanation tonometry, to identify the patients with normal tension glaucoma. (13) POAG patients with elevated intraocular pressure, correlated visual field loss, and glaucomatous optic nerve head changes criteria. (14) Glaucoma patients included in the study had a diagnosis of POAG or XFG. Structural definition: vertical cup-to-disc ratios (C/D) of 0.7 or more, asymmetry in the C/D of 0.2 or more, and/or thinning of the neuroretinal rim-to-disc ratio of less than 0.1 with corresponding perimetric damage. The Disc Damage Likelihood Scale system was used to evaluate the rim-to-disc ratio. Functional definition: the glaucoma hemifield test outside normal limits, and three adjacent points in the 5% level on the pattern deviation plot, using the 24–2 strategy of the Humphrey perimeter Visual fields were considered reliable if false-negative and false-positive responses were below 33%. Unavailable visual fields were repeated on the same day. If the second visual field was also unreliable, inclusion was made only on the basis of structural damage. (15) For the diagnosis of XFS, only the presence of the material in the anterior surface of the lens was considered. This surface, with the pupil dilated, was carefully examined for the presence of exfoliative material, using the high magnification of the slit-lamp and adequate illumination. (16) Angles were wide open on gonioscopy. Vertical cup/disc ratio ranged from 0.80 to 0.99, showing severe glaucomatous optic nerve damage. (17) The diagnosis of PEX was made on slit-lamp examination following mydriasis and included the presence of typical pseudoexfoliation material on the anterior lens capsule and/or on the pupillary border. PG patients were diagnosed when anterior segment findings of PEXG associated an IOP ≥21 mmHg without treatment, typical optic nerve head changes, and visual field defects. (18) The diagnosis of PEX syndrome was diagnosed if clinical examination revealed deposition of PEX material on the anterior lens capsule or at the pupillary border, the presence of transillumination defects near the pupil accompanied by normal optic nerve head finding, and intraocular pressure (IOP) less than 21 mmHg.

[20, 34, 37, 38, 40]. The TAS of the EXG group was lower than that of the control group in our meta-analysis, which is consistent with the results that had been reported. It has been shown that oxidative damage in connective tissues such as collagen and elastin can lead to the deposition of extracellular fibrillar [13, 14], which may be the pathogenesis of EXG. However, we did not find significant differences in the blood TAS, aqueous humor TAS, and aqueous humor TOS. The results of other studies that investigated TAS or TOS in aqueous humors remain under debate [20, 24, 38]. The difference may be explained by different study populations and detection methods.

There are several potential limitations of our study. First, we only included studies that scored at least a three in our quality assessment, thus excluding PACG, NTG, and other markers relevant to glaucoma that do not comprehensively
| Study name          | Difference in means | Standard error | Variance | Lower limit | Upper limit | Z value | p value |
|---------------------|---------------------|----------------|----------|-------------|-------------|---------|---------|
| Asaad A. Ghanem (2010) | 18.010              | 1.030          | 1.061    | 15.991      | 20.029      | 17.484  | 0.000   |
| S.M. Ferreira (2009)  | 15.000              | 1.166          | 1.360    | 12.714      | 17.286      | 12.862  | 0.000   |
| Sandra M. Ferreira (2005) | 15.200             | 0.561          | 0.314    | 14.101      | 16.299      | 27.118  | 0.000   |
| Amita Goyal (2014)    | 24.490              | 1.532          | 2.347    | 21.487      | 27.493      | 15.986  | 0.000   |

**Figure 2:** The meta-analysis of blood TAS levels in the OAG group.

| Study name          | Difference in means | Standard error | Variance | Lower limit | Upper limit | Z value | p value |
|---------------------|---------------------|----------------|----------|-------------|-------------|---------|---------|
| Asaad A. Ghanem (2010) | 14.910              | 0.518          | 0.269    | 13.894      | 15.926      | 28.773  | 0.000   |
| S.M. Ferreira (2009)  | 10.000              | 0.721          | 0.520    | 8.587       | 11.413      | 13.868  | 0.000   |
| Sandra M. Ferreira (2005) | 12.300             | 0.525          | 0.275    | 11.271      | 13.329      | 23.437  | 0.000   |
| Amita Goyal (2014)    | 12.410              | 0.794          | 0.631    | 10.853      | 13.967      | 15.621  | 0.000   |

**Figure 3:** The meta-analysis of aqueous humor SOD levels in the OAG group.

| Study name          | Difference in means | Standard error | Variance | Lower limit | Upper limit | Z value | p value |
|---------------------|---------------------|----------------|----------|-------------|-------------|---------|---------|
| Asaad A. Ghanem (2010) | 0.630               | 0.025          | 0.001    | -0.679      | -0.581      | -25.290 | 0.000   |
| Khaled K. Abu-Amero (2013) | -0.300             | 0.045          | 0.002    | -0.588      | -0.412      | -11.119 | 0.000   |
| Mesut Erdurmus (2011)  | -0.600              | 0.066          | 0.004    | -0.730      | -0.470      | -9.024  | 0.000   |

**Figure 4:** The meta-analysis of aqueous humor GPX levels in the OAG group.

| Study name          | Difference in means | Standard error | Variance | Lower limit | Upper limit | Z value | p value |
|---------------------|---------------------|----------------|----------|-------------|-------------|---------|---------|
| Asaad A. Ghanem (2010) | -0.030              | 0.073          | 0.598    | -1.545      | 1.485       | -0.039  | 0.969   |
| S.M. Ferreira (2009)  | 4.000               | 1.612          | 2.600    | 0.840       | 7.160       | 2.481   | 0.013   |
| Sandra M. Ferreira (2005) | 2.000              | 2.021          | 4.083    | -1.961      | 5.961       | 0.990   | 0.322   |
| Amita Goyal (2014)    | 3.210               | 1.229          | 0.366    | 0.043       | 2.414       | 2.031   | 0.042   |

**Figure 5:** The meta-analysis of aqueous humor CAT levels in the OAG group.
demonstrate oxidative stress. Second, most studies evaluated oxidative stress markers in aqueous humors by comparing them to groups with cataracts, which may also involve oxidative stress [51]. Third, our sensitivity analysis revealed some studies influenced the results, especially in the EXG patients. The present data should therefore be interpreted with caution and requires further confirmation in a larger clinical study.

In conclusion, considering the importance of oxidative stress in glaucoma and despite the limitations indicated above, this meta-analysis evaluated all the studies reporting the level of oxidative and antioxidative markers in aqueous humor or serum samples from glaucoma patients, making the results of our study more meaningful. Our study further verified the abnormality of oxidative stress markers in glaucoma. However, reports on the damage of oxidative stress in other eye tissues relevant to glaucoma are still few. Therefore, further research focusing on different aspects will help to provide a comprehensive understanding of oxidative stress in glaucoma. On the other hand, since peripheral blood is easy to collect and has been confirmed to show oxidative stress markers in patients with glaucoma,
| Study name                  | Sample            | Difference in means | Standard error | Lower limit | Upper limit | Z value | p value |
|----------------------------|-------------------|---------------------|----------------|-------------|-------------|---------|---------|
| Esra Ergan (2016)          | Blood             | 2.980               | 3.512          | 12.338      | 9.864       | 0.848   | 0.396   |
| Feyza Dursun (2015)        | Blood             | 1.690               | 0.206          | 0.043       | 1.286       | 2.094   | 8.198   |
| Emrullah Beyazyildiz (2014)| Blood             | 27.200              | 8.472          | 71.781      | 10.594      | 43.806  | 3.210   |
|                            | Aqueous humor     | 6.358               | 4.254          | 18.093      | -1.979      | 14.695  | 1.495   |

**Table 6: Sensitivity analysis using the leave-one-out strategy.**

| Study omitted              | Sample            | Z value | 95% CI       | p value |
|----------------------------|-------------------|---------|--------------|---------|
| OAG (total antioxidant status) | Blood             | 11.084  | -0.633 to -0.433 | <0.001  |
| Ahmed Mousa (2015)         | Blood             | 15.206  | 10.097 to 13.085 | <0.001  |
| Khaled K. Abu-Amero (2013) | Blood             | 14.255  | 11.422 to 15.064 | <0.001  |
| Mesut Erdurmus (2011)      | Aqueous humor     | 5.050   | 3.059 to 7.021  | <0.001  |
| Asaad A. Ghanem (2010)     | Aqueous humor     | 15.206  | 10.097 to 13.083 | <0.001  |
| S.M. Ferreira (2009)       | Aqueous humor     | 26.848  | -0.672 to -0.581 | <0.001  |
| Sandra M. Ferreira (2005)  | Aqueous humor     | 13.455  | 3.526 to 4.728  | <0.001  |
| Amita Goyal (2014)         | Aqueous humor     | 9.213   | 9.793 to 15.086  | <0.001  |

**Figure 9: The meta-analysis of aqueous humor TAS levels in the EXG group.**

OAG: open-angle glaucoma; EXG: exfoliative glaucoma; SOD: superoxide dismutase; GPX: glutathione peroxidase; CI = confidence interval. *The influenced meta-analysis results regarding the association of oxidative stress with OAG and EXG.
systemically monitoring the changes in oxidative stress markers may provide new ideas for the prevention and treatment of glaucoma.

**Conflicts of Interest**

All authors declare that there are no conflicts of interest.

**Authors’ Contributions**

Binghua Tang and Shengjie Li contributed equally to this paper.

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**Supplementary Materials**

Supplementary Figure 1: funnel plot analysis to detect publication bias between the blood TAS level in the OAG group, and the result suggested that no publication bias existed in these studies. Supplementary Figure 2: funnel plot analysis to detect publication bias between aqueous humor SOD levels in the OAG group, and the result suggested that no publication bias existed in these studies. Supplementary Figure 3: funnel plot analysis to detect publication bias between aqueous humor GPX levels in the OAG group, and the result suggested that no publication bias existed in these studies. Supplementary Figure 4: funnel plot analysis to detect publication bias between aqueous humor CAT levels in the OAG group, and the result suggested that no publication bias existed in these studies. Supplementary Figure 5: funnel plot analysis to detect publication bias between blood TAS levels in the EXG group, and the result suggested that there no publication bias existed in these studies. Supplementary Figure 6: funnel plot analysis to detect publication bias between blood TOS levels in the EXG group, and the result suggested that no publication bias existed in these studies. Supplementary Figure 7: funnel plot analysis to detect publication bias between aqueous humor TAS levels in the EXG group, and the result suggested that no publication bias existed in these studies. Supplementary Figure 8: funnel plot analysis to detect publication bias between aqueous humor TOS levels in the EXG group, and the result suggested that no publication bias existed in these studies. (Supplementary Materials)

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