Triglycerides and Open Angle Glaucoma – A Meta-analysis with meta-regression

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Although intraocular pressure is the main risk factor for the development of glaucoma, other risk factors such as vascular dysfunction might play an additional pathogenic role. Hypertriglyceridemia, which may lead to vascular dysfunction, has been implicated in the development of glaucoma. The objective of this meta-analysis was to investigate the association of triglyceride levels with the risk of glaucoma in case-control studies. Seventeen case-control studies were included investigating the difference in triglyceride levels in patients with glaucoma (N = 1,391) compared to subjects without glaucoma (N = 25,575). In random effects meta-analysis, the pooled mean triglyceride level across all studies and patients with and without glaucoma was 132.9 mg/dL (95%CI: 124.0–141.7). Patients with glaucoma had significantly higher mean triglyceride levels than patients without glaucoma (absolute difference = 14.2 mg/dL, 95%CI: 5.8–22.5, p < 0.0001). A considerable amount of heterogeneity of included studies was observed (I² = 66.2%, heterogeneity χ² = 47.4 on 16 degrees of freedom, p < 0.0001). In conclusion, this meta-analysis of case-control studies found that patients with glaucoma had higher mean triglyceride levels than patients without glaucoma. This finding is consistent with the concept that hypertriglyceridemia represents an additional risk factor for glaucoma. Whether this association is causal and/or might be modified by glaucoma medications remains to be investigated.

Elevated intra-ocular pressure (IOP) is the main risk factor for the development of glaucoma. However, many patients develop glaucoma despite an IOP in the normal range, and not all patients with elevated IOP develop glaucoma. Therefore, other risk factors have been implicated in the pathogenesis of glaucoma including structural abnormalities and functional dysregulation of the vasculature supplying the optic nerve and the surrounding retinal tissue. The presence of vascular dysfunction in glaucoma patients was recently postulated in a large clinical study, the Leuven Eye Study.

Hypertriglyceridaemia is often seen in patients with metabolic syndrome and type 2 diabetes. Based on recent genetic studies, triglycerides are increasingly considered to be a causal cardiovascular risk factor. Thus, novel therapies to reduce circulating triglycerides are currently being developed. The role of triglycerides in the pathogenesis and progression of glaucoma remains unclear. Several case-control studies report a significant association of triglycerides with glaucoma and with intraocular pressure. However, this was not confirmed in all studies and a recent study by Ko et al. even found a significant inverse relationship between high triglyceride levels and glaucoma. The objective of this meta-analysis was to investigate the association of triglyceride levels with the risk of glaucoma in case-control studies.

Results
Study characteristics. Seventeen studies were included investigating the difference in triglyceride levels in patients with glaucoma (number of patients (N) 1,391) compared to patients without glaucoma (N 25,575) (Table 1).
The largest study included 300 patients with normal tension glaucoma (NTG) and 17940 patients without glaucoma, while the smallest study included 19 patients with pseudoxfoliation glaucoma (PEX) glaucoma and 51 patients without glaucoma. Five studies included patients with primary open angle glaucoma (POAG), five studies patients with NTG, two studies patients with PEX glaucoma, two studies patients with NTG and POAG, one study patients with NTG and PEX glaucoma and two studies included all glaucoma types. Patients without glaucoma were hospital controls in six studies, community controls in four studies and not defined in seven studies (Table 2).

### Table 1. Triglyceride summary statistics of the 17 included studies.

| Study       | Glaucoma | N_p | N_c | Triglycerides_p | Triglycerides_c | p-value | TotalChol_p | TotalChol_c | LDL_p | LDL_c | HDL_p | HDL_c |
|-------------|----------|-----|-----|-----------------|-----------------|---------|-------------|-------------|-------|-------|-------|-------|
| Yilmaz      | NTG      | 33  | 40  | 145             | 121             | 0.02    | 221.5       | 191         | 138.3 | 123.2 | 47.1  | 42.8  |
| Ogurel      | PEX      | 19  | 16  | 192.1           | 260.7           | 0.44    | 191.2       | 212.8       | 107.1 | 119.6 | 47.5  | 42.8  |
| Shin        | NTG      | 55  | 92  | 174.9           | 141             | 0.51    | 164.8       | 161.1       |       |       |       |       |
| Modrzejewska | NTG   | 56  | 54  | 110.4           | 97.9            | 0.1     | 200.2       | 165.2       | 83.3  | 38.3  | 44.1  |       |
| Kurtul      | PEX      | 20  | 52  | 145             | 140             | 0.92    | 220         | 217.39      | 150   | 38.3  | 44.4  |       |
| Bossuyt     | NTG      | 30  | 33  | 94              | 98              | 0.72    | 201         | 215         | 111   | 120   | 69    | 75    |
| Zhao        | Glaucoma | 191 | 2835| 154             | 145.6           | 0.52    | 155.4       | 155.5       |       |       |       |       |
| Kim         | NTG      | 300 | 17940| 128            | 120.2           | 0.37    | 54.3        | 53          |       |       |       |       |
| Kim#1       | OAG      | 80  | 4015| 112.2           | 112.3           | 0.79    | 178         | 176.5       |       |       |       |       |
| Davar       | POAG     | 40  | 40  | 165.9           | 99.5            | <0.01   | 211.2       | 162.3       |       |       |       |       |
| Lee         | NTG      | 45  | 35  | 170.4           | 148             | 0.34    | 203.8       | 207.9       | 120.7 | 124.6 | 59.1  | 60    |
| Yuki        | NTG      | 43  | 40  | 146.6           | 128.9           | 0.34    | 224.5       | 216         |       |       |       |       |
| Engin       | Glaucoma | 160 | 31  | 170.5           | 118             | N/d     | 201.2       | 173         |       |       |       |       |
| Pavlijevic   | POAG     | 50  | 50  | 210.6           | 180.5           | N/a     | 237         | 230         | 152.9 | 157.5 | 56    | 54    |
| Choe        | NTG      | 38  | 38  | 114.8           | 108.1           | 0.68    | 167.5       | 181         | 107.9 | 118.3 | 53.1  | 54.9  |
| Chiba       | POAG     | 20  | 105 | 0                | 86              | Ns       | 204         | 214         |       |       |       |       |
| Elisaf       | POAG     | 49  | 72  | 145.3           | 152.7           | Ns       | 233.7       | 237.5       | 160   | 156   | 50.6  | 51.8  |

The largest study included 300 patients with normal tension glaucoma (NTG) and 17940 patients without glaucoma, while the smallest study included 19 patients with pseudoxfoliation glaucoma (PEX) glaucoma and 51 patients without glaucoma. Five studies included patients with primary open angle glaucoma (POAG), five studies patients with NTG, two studies patients with PEX glaucoma, two studies patients with NTG and POAG, one study patients with NTG and PEX glaucoma and two studies included all glaucoma types. Patients without glaucoma were hospital controls in six studies, community controls in four studies and not defined in seven studies (Table 2).

### Triglyceride levels in patients with and without glaucoma.

In random-effects meta-analysis of all 17 included studies, the mean triglyceride level pooled across studies and patients with and without glaucoma was 132.9 mg/dL (95% CI: 124.0–141.7, Table 1, Supplementary Figure 1). The mean triglyceride level strongly varied between studies (I² = 91.9%, heterogeneity χ² = 197.1 on 16 degrees of freedom, p < 0.0001), and ranged from 93.3 mg/dL in the study by Chiba et al. to 223.5 mg/dL in the study by Ogurel et al. Patients with glaucoma had higher mean levels of triglycerides than patients without glaucoma. In detail, the pooled mean absolute difference in triglycerides between patients with and without glaucoma was 14.2 mg/dL in random-effects analysis (95% CI: 5.8–22.5, p < 0.0001, Fig. 1), and 13.0 mg/dL in fixed-effects analysis (95% CI: 8.9–17.0, p < 0.0001, Fig. 1). Upon inspection of study weights (gray boxes in Fig. 1), we observed that only 2 studies (Kim et al. #2, 2014, and Yilmaz et al. 2016) contributed half of the information to the pooled difference in triglycerides. On a standardized mean difference (SMD) scale, patients with glaucoma had a 0.21 standard deviations (SD) higher triglyceride level than patients without glaucoma (95% CI: 0.09–0.34, p < 0.0001, Supplementary Figure 2). The corresponding fixed-effects estimate was 0.15 SD (95% CI: 0.08–0.22, p < 0.0001).

In cumulative meta-analysis, we found that significantly higher mean triglyceride levels were consistently found after the study of Lee et al., which appeared in 2012 (Fig. 2).

In both meta-analyses of absolute and standardized mean triglyceride differences between patients with glaucoma and controls, we observed statistically significant evidence for heterogeneity (I² = 66.2%, heterogeneity χ² = 47.4 on 16 degrees of freedom, p < 0.0001). This finding suggests that random effects estimates may be more appropriate than fixed effects estimates. Further, this relative large heterogeneity estimate is consistent with the assumption that other between-study differences may at least partly explain the overall difference in triglyceride levels between glaucoma patients and controls. To explore these potential factors, we performed a meta-regression (Table 3). In detail, we investigated the covariables age, sex, diabetes, BMI, LDL cholesterol, HDL cholesterol, total cholesterol, systolic blood pressure, diastolic blood pressure, and mean within-study triglyceride levels. None of these variables were significantly associated with the difference in triglycerides between patients with and without glaucoma, except for HDL, which was "borderline statistically significantly" associated with the triglyceride difference. However, considering that (1) meta regression
| Study     | Patients | Controls | Inclusion of                              |
|-----------|----------|----------|------------------------------------------|
|           | Number   | Type     | Definition                                | Number | Definition                                      | Hospital-based | Diabetics | Smokers | Cardiovascular disease | Lipid-lowering medication | Triglycerides as primary Endpoint |
|          |          |          |                                          |        |                                              |                |           |         |                               |                             |                                      |
| Yilmaz37  | 32       | NTG      | ≤21 mmHg + glaucomatous changes in the optic disc and visual field | 40     | 21 mmHg + NO glaucomatous changes in optic disc and visual field | N/d           | Yes       | No     | Yes                           | N/d                          | Yes                                    |
|          | 31       | PEX-Glaucoma | Presence of pseudoexfoliation material + >21 mmHg + glaucomatous changes in the optic disc and visual field |        | Presence of pseudo-exfoliation material + ≤21 mmHg | No             | No        | No     | N/d                          | N/d                          | No                                    |
| Ogurel38  | 19       | PEX-Glaucoma | Presence of pseudoexfoliation material + >21 mmHg | 16     | No                                           | N/d           | No        | No     | N/d                          | No                           | No                                    |
|          |          |          |                                          |        |                                              |                |           |         |                               |                             |                                      |
| Shim39    | 55       | NTG      | ≤21 mmHg + glaucomatous changes in the optic disc and visual field | 92     | N/d                                           | Yes           | ONLY Diabetics | N/d | N/d                          | No                           | No                                    |
|          | 20       | POAG     | >21 mmHg + glaucomatous changes in the optic disc and visual field + open-angle on gonioscopy | 54     | N/d                                           | N/d           | No        | No     | N/d                          | N/d                          | No                                    |
| Modrzejewska40 | 56 | POAG     | Glaucomatous changes in the optic disc, visual field and scanning laser polarimeter |        |                                              |                |           |         |                               |                             |                                      |
| Kurtul21  | 20       | PEX-Glaucoma | Presence of pseudoexfoliation material + >21 mmHg + glaucomatous changes in the optic disc and visual field + open-angle on gonioscopy | 52     | Presence of pseudo-exfoliation material + ≤21 mmHg | N/d           | Yes       | N/d | Yes                           | No                           | Yes                                    |
|          |          |          |                                          |        |                                              |                |           |         |                               |                             |                                      |
| Bossuyt41  | 30      | NTG      | ≤21 mmHg + glaucomatous changes in the optic disc and visual field | 33     | N/d                                           | No             | No        | No     | N/d                          | No                           | Yes                                    |
| Zhao19    | 191     | Glaucoma | Self-reported                            | 2835   | Self-reported                                 | No             | Yes       | Yes | N/d                          | N/d                          | No                                    |
| Kim #240 | 300     | NTG      | ≤21 mmHg + glaucomatous changes in the optic disc and visual field | 17940  | N/d                                           | No             | Yes       | No     | N/d                          | Yes                          | Yes                                    |
| Kim #141 (risk factors) | 80 | OAG     | >21 mmHg or glaucomatous changes in the optic disc or optic disc haemorrhage or presence of retinal nerve fibre layer defect | 4015   | ≤21 mmHg + NO glaucomatous changes in optic disc + open angle + absence of disc haemorrhage + absence of retinal nerve fibre layer defect + optic disc satisfying the ISNT rule  | No             | Yes       | N/d | N/d                          | N/d                          | Yes                                    |
| Davari, 2014 | 40 | POAG     | N/d                                       | 40     | N/d                                           | Yes            | No        | No     | No                           | No                           | Yes                                    |
| Lee42     | 45       | NTG      | ≤21 mmHg + glaucomatous changes in the optic disc and visual field + open anterior chamber by gonioscopy | 35     | N/d                                           | Yes            | No        | N/d | No                           | No                           | No                                    |
| Yuki43    | 43       | NTG      | ≤21 mmHg + glaucomatous changes in the optic disc and/or presence of nerve fibre layer defect + open anterior chamber by gonioscopy | 40     | ≤21 mmHg + NO glaucomatous changes in the optic disc | Yes            | No        | No     | N/d                          | No                           | No                                    |
| Engin44   | 160     | Glaucoma | ≤21 mmHg and/or glaucomatous changes in the optic disc and/or visual field | 31     | N/d                                           | N/d           | N/d        | N/d | N/d                          | N/d                          | No                                    |
| Pavljasevic45 | 50 | POAG     | N/d                                       | 50     | N/d                                           | Yes            | N/d        | N/d | N/d                          | N/d                          | Yes                                    |

Continued
Table 2. Characteristics of the 17 included studies. aN/d: Not defined. bControl patients were recruited from medical staff and clinic patients.

| Study  | Patients | Controls | Inclusion of |
|--------|----------|----------|--------------|
|        | Number   | Type     | Definition   | Number | Definition          | Hospital-based | Diabetics | Smokers | Cardiovascular disease | Lipid-lowering medication | Triglycerides |
|        |          |          |             |         |                     |               |           |         |                     |                          | as primary Endpoint |
| Choi  | 38       | NTG      | ≤21 mmHg + glaucomatous changes in the optic disc and visual field + open anterior chamber by gonioscopy | 38     | ≤21 mmHg + NO glaucomatous changes in the optic disc and visual field + NO disc haemorrhage, notching, excavation or asymmetry of the vertical cup to disc ratio > 0.2 | Yes a | No | N/d | No | No | Yes |
| Chiba | 31       | NTG      | N/d         | 61     | N/d                  | No | Yes | No | No | No | |
|        | 20       | POAG     | N/d         |         |                      | No | Yes | No | No | No | |
| Elisa  | 49       | POAG     | Glaucomatous changes in the optic disc and visual field + open anterior chamber by gonioscopy | 72     | Normal intraocular pressure | N/d | Yes | Yes | No | No | Yes |

Discussion

In this meta-analysis of 1391 patients with glaucoma compared to 25,575 without glaucoma included in 17 cross-sectional studies, we found higher mean triglyceride levels in patients with glaucoma compared to controls. The pooled mean absolute difference in triglycerides between patients with and without glaucoma was 1.42 mg/dL.

The association of triglycerides and glaucoma has so far been a matter of ongoing debate. Some studies found a significant association, while others could not confirm this association. These different results are reflected by the considerable amount of heterogeneity found in this meta-analysis. One reason for this heterogeneity may be that different types of glaucoma were included in this meta-analysis. Furthermore, inclusion criteria were different among the included studies. For example, visual field defects had to be present in some but not all studies. Three studies had no definition for who was considered to be a patient with glaucoma and in one study patients were simply surveyed on whether they had a glaucoma. The control groups were equally dissimilar. Six studies included hospital controls, four community controls and seven did not report on control group recruitment. Nine studies gave no definition of the inclusion criteria for the control group. Likewise, exclusion criteria were different among the included studies. This may be particularly relevant for a modifying influence of co-medications on triglyceride levels. For example, patients using lipid-lowering medication were excluded in six of the 17 studies and included in one study, while the other 10 studies did not report any data on the use of lipid-lowering medication. Moreover, diabetes mellitus, smoking and cardiovascular disease was included in some studies, excluded in others, or not reported on (Table 2).

However, not only co-medications may modify the association of triglycerides and glaucoma, but also medications used for glaucoma treatment. Importantly, topical beta-blockers, which are a cornerstone treatment for glaucoma, have been shown to increase systemic triglyceride levels in a study on 28 healthy volunteers taking topical timolol. Given the fact that it is very likely that the patients in this meta-analysis had a high prevalence of topical beta-blocker use, this may have increased the difference in triglyceride levels between patients and controls. Therefore, future studies should address this potential bias.
In meta-regression, we found that HDL cholesterol was a modifier of the glaucoma-triglyceride-association. Specifically, studies including patients with lower average HDL cholesterol levels showed larger differences in triglyceride levels between patients with and without glaucoma. As HDL levels are known to inversely correlate with triglyceride levels, suggesting a dynamic interaction, it seems rather unlikely that HDL itself is a modifier of the glaucoma-triglyceride-association. We hypothesize that lipid-lowering interventions may cause this surprising result. In a recent meta-analysis, statin use was associated with a reduced incidence of glaucoma. Life-style interventions influencing the metabolism of HDL such as smoking, weight loss and physical activity, and the use of lipid-lowering medications are poorly reported in most studies. For example, the percentage of patients using lipid-lowering medications was given, which might also explain the inverse correlation. Further no information on the use of lipid-lowering drugs, especially fibrates, is given, which might also explain the inverse correlation.

Table 3. Meta regression models exploring potential determinants of the difference in triglyceride levels between patients with and without glaucoma. Covariables were centred at or close to their mean across studies.

| Model   | N of studies | Variable                                      | Estimate of triglyceride difference (mg/dL) | 95%CI         | p         | Base model I² | Residual I² |
|---------|--------------|-----------------------------------------------|------------------------------------------|--------------|-----------|---------------|-------------|
| Base Model | 17           | Constant*                                      | 14.48                                    | 3.97–24.98   | 0.010     | 66.3%         | N/A         |
| Model #1 | 17           | Age (per 5 years increase above 60)            | −0.54                                    | −6.24–5.17   | 0.843     | 66.3%         | 68.3%       |
|          |              | Constant*                                      | 14.26                                    | 2.82–25.71   | 0.018     |               |             |
| Model #2 | 16           | Female sex (per 10% increase in prevalence above 50% prevalence) | −0.76                                    | −9.89–8.36   | 0.860     | 68.4%         | 70.4%       |
|          |              | Constant*                                      | 15.23                                    | 2.35–28.12   | 0.024     |               |             |
| Model #3 | 5            | Diabetes (per 10% increase in prevalence of 15% prevalence) | 8.74                                     | −17.34–34.82 | 0.364     | 51.8%         | 37.6%       |
|          |              | Constant*                                      | 10.00                                    | −8.48–28.48  | 0.184     |               |             |
| Model #4 | 10           | BMI (per 1 kg/m² increase above 25 kg/m²)      | −0.33                                    | −4.65–3.99   | 0.866     | 45.7%         | 43.0%       |
|          |              | Constant*                                      | 6.92                                     | −2.72–16.56  | 0.137     |               |             |
| Model #5 | 9            | LDL cholesterol (per 10 mg/dL increase above 120 mg/dL) | −0.20                                    | −7.19–6.79   | 0.948     | 43.3%         | 50.3%       |
|          |              | Constant*                                      | 7.79                                     | −4.67–20.35  | 0.186     |               |             |
| Model #6 | 12           | HDL cholesterol (per 10 mg/dL increase above 50 mg/dL) | −5.92                                    | −12.55–0.71  | 0.075     | 30.4%         | 4.2%        |
|          |              | Constant*                                      | 9.30                                     | 3.69–14.91   | 0.004     |               |             |
| Model #7 | 15           | Total cholesterol (per 10 mg/dL increase above 200 mg/dL) | −2.32                                    | −9.00–4.37   | 0.468     | 69.3%         | 70.6%       |
|          |              | Constant*                                      | 16.33                                    | 3.55–29.12   | 0.016     |               |             |
| Model #8 | 7            | Systolic blood pressure (per 10 mmHg increase above 125 mmHg) | −5.89                                    | −26.15–14.37 | 0.489     | 0.0%          | 0.0%        |
|          |              | Constant*                                      | 6.95                                     | −4.12–18.03  | 0.167     |               |             |
| Model #9 | 7            | Diastolic blood pressure (per 10 mmHg increase above 75 mmHg) | −4.80                                    | −30.98–21.38 | 0.657     | 0.0%          | 0.0%        |
|          |              | Constant*                                      | 9.78                                     | 0.34–19.22   | 0.045     |               |             |
| Model #10| 17           | Mean within-study triglyceride level (per 10 mg/dL increase above 130 mg/dL) | 1.72                                     | −2.15–5.59   | 0.358     | 66.3%         | 62.6%       |
|          |              | Constant*                                      | 14.34                                    | 3.84–24.85   | 0.011     |               |             |
Hypertriglyceridemia is known to be a risk factor for glaucoma, as hypertriglyceridemia. Glaucoma medication has also been suggested to influence lipid levels, however evidence is very limited.

**Figure 1.** Random-effects meta-analysis of triglyceride level differences between patients with glaucoma and controls. The differences are expressed on an absolute scale, i.e. they represent differences in mg/dL. “I-V Overall” represents the fixed effects pooled estimate, and “D+L Overall” the random-effects pooled estimate. Grey boxed surrounding the individual study estimates are proportional to the fixed effects weight of the study. Diamonds surrounding the pooled estimates represent 95% confidence intervals. Abbreviations: 95%CI - 95% confidence interval, SD - Standard Deviation.

**Figure 2.** Cumulative meta-analysis of triglyceride level differences between patients with glaucoma and controls. Studies are sorted by calendar time. The estimates represent cumulative mean absolute differences in triglyceride levels (in mg/dL) between patients with glaucoma and controls. After the study of Lee et al., which appeared in 2012, all cumulative difference estimates indicate a statistically significantly higher average triglyceride level in glaucoma patients.
Finally, we want to mention three limitations of the study. First, the current analysis only incorporates observational data. Therefore, we want to stress that although our study provides strong statistical evidence that differences in triglyceride levels between glaucoma patients and controls are strongest in patient populations with low average HDL levels.

**Figure 3.** Random-effects meta-regression of triglyceride level differences between patients with glaucoma and controls according to within-study mean high-density-lipoprotein (HDL) levels. The red line represents a line of best fit from meta-regression. The diameter of the hollow circles reflects the weight of the individual studies in the random-effects meta-regression. The slope of the line of best fit declines with increasing HDL levels, which suggests that differences in triglyceride levels between glaucoma patients and controls are strongest in patient populations with low average HDL levels.

**Figure 4.** Prisma Flow Diagram of the study selection process. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit http://www.prisma-statement.org.
triglycerides are associated with glaucoma, we cannot prove causality. Specifically, we cannot answer whether hypertriglyceridemia leads to glaucoma via a potential effect on intraocular pressure, or whether triglycerides may have a pathogenic impact on glaucoma independently of intraocular pressure. Second, the observational nature of the included studies does not allow us to evaluate whether interventions that lower triglyceride levels can modify glaucoma development and/or outcomes. Randomised clinical studies are needed to investigate whether the use of triglyceride-lowering drugs may be useful in the prevention or treatment of glaucoma. Preliminary evidence supporting a role for lipid-lowering drugs towards glaucoma outcomes stems from a large British registry study, in which statin use was associated with lower IOP\textsuperscript{35}. This is relevant also for our meta-analysis, given the fact that statins not only lower LDL cholesterol but also triglyceride levels, which may in turn ameliorate the adverse association of triglycerides with glaucoma. Although the impact of statins on IOP did not prevail after adjusting for beta-blockers in the aforementioned study, future studies should clearly explore how lipid-lowering drugs affect triglyceride levels and their role on glaucoma development and progression. Third, we obtained convincing statistical evidence that patients with glaucoma have higher average triglyceride levels than controls. However, it remains to be investigated whether this statistically significant absolute difference of approximately 14 mg/dL is not only statistically significant but also clinically relevant. This question could be addressed by future studies, which employ a prospective design looking at clinical outcomes of glaucoma pathogenesis or glaucoma progression.

In conclusion, our meta-analysis summarizes a large body of evidence from case-control studies on the glaucoma–triglyceride association. The observed results are consistent with the concept that hypertriglyceridemia may contribute to glaucoma pathogenesis, and support the future conduct of randomized trials on triglyceride-lowering interventions for prevention or treatment of glaucoma.

**Methods**

**Search history.** From July 12\textsuperscript{th}, 2014, until August 2\textsuperscript{nd}, 2016, we used an Ovid Interface to search for the following medical subject headings in the databases PubMed, EMBASE, and The Cochrane Library: “glaucoma” AND “triglycerides”; “intraocular pressure” AND “triglycerides”; “glaucoma” AND “dyslipidemia”; and “intraocular pressure” AND “dyslipidemia”. The reference lists of included studies were additionally scanned to identify potentially relevant reports. Two investigators (LP & FP) performed the literature search and study selection.

Studies were included if they reported the triglyceride levels in patients with glaucoma and compared to control patients. Only studies in English language were included. All abstracts and conference proceedings that are not published in peer-reviewed journals were excluded. If original data or exact numbers were not available, they were not included in the quantitative analysis (Fig. 4).

**Statistical methods.** All statistical analyses were performed using Stata (Windows version 14.0, Stata Corp., Houston, TX, USA). Differences in mean triglyceride levels between patients with and without glaucoma were analysed using random- and fixed-effects meta-analysis (Stata routine metan). Differences were analysed both on an absolute scale (i.e. difference in triglycerides between patients with and without glaucoma in mg/dL) and on a standardized scale (i.e. difference in triglycerides between the two groups in units of standard deviation (so-called standardized mean differences)). The I\textsuperscript{2} statistic was evaluated for quantifying the extent of unexplained variation in the triglyceride-glaucoma association (i.e. heterogeneity). The user–contributed suite metacum was applied for cumulative meta-analysis of absolute differences in triglyceride levels between patients with and without glaucoma. Meta-regressions were performed on the absolute scale with Stata’s user-contributed routine metareg in order to explore potential modifiers of the triglyceride-glaucoma association. The full analysis code is available on request from FP.

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L.P. and E.P. performed the literature search and wrote the main manuscript. E.P. performed the statistical analysis. G.M., A.W., M.W., O.K. and G.S. reviewed the manuscript.

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