# The retinal ganglion cells in metabolic syndrome

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The retinal ganglion cells (RGCs) are particularly prone to glaucomatous damage, usually inflicted by mechanical stress to the optic nerve due to high intraocular pressure (IOP), eventually leading to irreversible visual field deterioration. Nevertheless, additional factors contributing to RGC loss have been identified, the most important among whom being aging and insufficient vascular supply. In this regard, metabolic syndrome is a cluster of systemic conditions with microvascular complications that have been suggested by several studies as risk factors for RGC ischemic injury, namely dyslipidemia, hyperglycemia, and arterial hypertension (AH).

Baek *et al.* conducted a study investigating the association between metabolic syndrome components and nonglaucomatous, localized retinal nerve fiber layer (RNFL) defects in adults of Asian origin, up to 85 years of age (1). The main strength of this study was the large sample size (n=17,591) allowing for a 1:5 propensity matching of 238 cases (presence of RNFL defects) with 1,190 controls (absence of RNFL defects). They reported that central obesity [odds ratio (OR): 1.53; 95% confidence intervals (CI): 1.11–2.13; P=0.01], elevated blood pressure (BP; OR =1.50; 95% CI: 1.09–2.05; P=0.01), and elevated fasting glucose (OR =1.42; 95% CI: 1.03–1.97; P=0.03) were all independently associated with the presence of RNFL defects, in multivariable logistic regression analysis, adjusted for age, sex, and IOP. They also reported that an increasing number of metabolic syndrome components present increased the odds for detection of RNFL defects (ORs ranging from 1.27 to 2.41, depending on the number of metabolic syndrome components present). A limitation of this study is the fact that RNFL defects were quantified solely from fundus photographs, lacking three-dimensional, high-resolution information derived from optical coherence tomography (OCT) scans. Global or sectoral RNFL thickness, assessed by OCT, is arguably a more informative metric, because it does not depend on subjective contrast perception and can also be accurately quantified. Another limitation is that solely color fundus images were used for outlining RNFL defects, which offer suboptimal contrast than red-free images. It is, therefore, possible that the reported 1.4% detectable RNFL defects in the screened population do not reflect the true prevalence.

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## Obesity and dyslipidemia

Previous population-based, cross-sectional studies in ophthalmologically healthy subjects or in the general population have reported mixed results regarding obesity and RGC structure, in multivariable models. The Singapore Epidemiology of Eye Diseases Study (SEEDS) found no association between body mass index (BMI) and OCT-derived RNFL thickness in 3 ophthalmologically healthy Asian populations (n=4,475, age 40–80 years). However, a positive association was found between low-density lipoproteins (LDL) and RNFL thickness [b=0.35 µm/(mmol/L); 95% CI: 0.06–0.65; P=0.02] (2). More recent data from the same population (n=10,049 eyes from 5,333 subjects) reported no association between obesity or dyslipidemic indices and ganglion cell-inner plexiform layer (GC-IPL) thickness (3). In a pooled analysis of 10 populations from the Asian Epidemiological Eye Consortium (n=22,436 nonglaucomatous subjects over 40 years old), higher BMI was associated with thicker OCT-derived RNFL [b=0.07 µm/(kg/m$^2$); 95% CI: 0.03–0.11; P<0.001] (4). In the Beijing Eye Study, the presence of localized RNFL defects was assessed in 3,097 Chinese subjects over 40 years old, using a similar fundus imaging-based approach to the one described by Baek *et al.* They reported that the presence of RNFL defects in the general population was associated with suprathreshold blood concentration of LDL (OR =1.42; 95% CI: 1.08–1.85; P=0.01) (5). When a heavily overlapping population was evaluated by means of OCT 5 years later (n=2,548 subjects over 50 years old), none of the obesity or dyslipidemic indices were found to be significantly associated with RNFL thickness (6).

Data from 8 meta-analyzed studies from the European Eye Epidemiology (E3) Population showed no association between BMI and OCT-derived RNFL thickness in the general population (n=16,084, mean age range 57–82 years). A borderline positive association was uncovered when glaucomatous individuals were excluded from the analysis [b=0.09 µm/(kg/m$^2$); 95% CI: 0.00–0.18; P=0.05] (7). In the EPIC-Norfolk Eye Study (n=11,030 eyes of 6,309 predominantly white participants, age 40–79 years), a negative association of very small effect size was observed between BMI and RNFL thickness, and only in male subjects [b=–0.30 µm/(5 kg/m$^2$); 95% CI: –0.58 to –0.02; P=0.039; n=4,812 eyes of 2,784 men], as assessed by the GDx nerve fiber analyzer (8). A similar finding was reported in the Tromso Eye Study (TES) [n=8,288, mean ± standard deviation (SD) age: 62±10 years], with OCT-derived RNFL thickness in men, but not women, correlating negatively with BMI [b=–0.26 µm/(5 kg/m$^2$); 95% CI: –0.41 to –0.11; P=0.001]. Neither body fat percentage nor lipoprotein concentrations were significantly associated with RNFL thickness in the same model. In the same study, GC-IPL thickness was associated with BMI both in men [b=–0.61 µm/(5 kg/m$^2$); 95% CI: –0.91 to –0.31; P<0.001] and women [b=–0.25 µm/(5 kg/m$^2$); 95% CI: –0.48 to –0.03; P=0.030]. In addition, GC-IPL thickness was associated with body fat percentage (b=–0.55 µm/10%-point; 95% CI: –0.97 to –0.15; P=0.010), but not with lipoprotein concentrations. TES also reported on the longitudinal association between obesity or dyslipidemic indices with RGC structure in 2,460 subjects. The only significant association uncovered was that of BMI with GC-IPL thickness [b=–0.17 µm/8 years/(5 kg/m$^2$); 95% CI: –0.32 to –0.01; P=0.033] (9). Last, a multiethnic study of ophthalmically healthy African Americans, Latino Americans, and Chinese Americans (n=11,585 eyes from 6,133 subjects over 50 years old) revealed no association between obesity or dyslipidemic indices and OCT-derived RNFL thickness (10).

A critical evaluation of the heterogeneous results raises the following points. First, almost all studies reporting significant associations between BMI and RGC structure have not adjusted the models for optic disc parameters or beta-zone peripapillary atrophy (β-PPA). On the other hand, all studies reporting absence of such associations have adjusted the multivariable models for at least some of those parameters. This suggests that there might exist a mediating or confounding effect of other structural parameters affected by obesity or dyslipidemic indices on RGC structure. Indeed, optic disc morphology is affected by anthropometric parameters and, in turn, can itself affect RNFL thickness and distribution (11). Additionally, larger β-PPA has been independently associated with increased BMI, a possible effect of lipid accumulation in and around retinal pigment epithelium (RPE) cells (12). Second, a confounding effect of statins is likely. Statins, the mainstay of dyslipidemic treatment, have been associated with lower risk of primary open-angle glaucoma (POAG) development, based on longitudinal studies, possibly owing to a neuroprotective effect exerted to the RGCs (13). Not all studies, however, confirm these findings (14). Last, all significant associations reported in the aforementioned large-scale population-based studies are of small effect size and are, therefore, unlikely to affect clinical decisions.

## Hyperglycemia

Reports on hyperglycemic status and RGC structure are also conflicting. In SEEDS, diabetes was associated with thinner RNFL (b=–0.67 µm; 95% CI: –1.32 to –0.02; P=0.04), but not GC-IPL (2,3). In the pooled analysis of the Asian Epidemiological Eye Consortium, diabetes was, again, associated with thinner RNFL [b=–0.72 µm; 95% CI: –1.20 to –0.24; P=0.003] (4). In the Beijing Eye Study, the presence of fundus image-derived localized RNFL defects was associated with coexistence of diabetic retinopathy (OR =3.20; 95% CI: 1.53–6.67; P=0.002), but OCT-derived global RNFL thickness and diabetes showed no association (5,6).

Diabetes was unrelated to RNFL thickness in the 8 meta-analyzed studies of the E3 population, regardless of whether glaucomatous individuals were included in the analysis (7). In TES, glycated hemoglobin (HbA1c) was not associated with RNFL or GC-IPL thickness at baseline, but it must be noted that diabetic individuals were excluded from this population. In the same study, lower HbA1c was associated with longitudinal RNFL thinning (b=0.31 µm/8 years/1%-point; 95% CI: 0.08–0.54; P=0.007) (9). Last, in the multiethnic study of American minorities, an association between diabetes and RNFL thinning was reported (b=–0.85 µm; 95% CI: –1.55 to –0.15; P=0.02) (10).

The following points are worthy of discussion. Most evidence points towards a negative effect of hyperglycemia on the RGCs, albeit this was not true in European populations. Although the reasons behind this observation are not clear, one could theoretically attribute it to genetic differences or to varying glycemic control standards and adherence between populations. Owing to the fact that RGC function is heavily glucose-dependent, the observation that lower HbA1c was associated with longitudinal RNFL thinning in TES, in the absence of diabetic individuals, could be potentially attributed to hypoglycemic nadirs or glucose fluctuations hampering RGC metabolism. Again, all significant associations reported in these large-scale studies are of small effect size. That being said, a case control study in a Greek population (n=211 eyes of 107 diabetic subjects, mean ± SD age: 65±9 years) showed that the magnitude of the effect is dependent on Hb1Ac levels, duration of diabetes, and diabetic retinopathy severity, suggesting a dose-response behavior of the reported associations (15).

## AH

SEEDS found no association between AH and RNFL or GC-IPL thickness (2,3). Data from the Asian Epidemiological Eye Consortium, however, revealed a negative association between AH and RNFL thickness (b=–0.68 µm; 95% CI: –1.04 to –0.32; P<0.001) (4). In the Beijing Eye Study, higher mean BP was associated with higher odds for presence of localized RNFL defects (OR =1.07 per 1 mmHg increase; 95% CI: 1.03–1.10; P<0.001) (5). Nevertheless, OCT-derived RNFL thickness was not associated with AH (6).

In the E3 meta-analyzed populations, AH was associated with a decrease in RNFL thickness, both in the general population (b=–0.54 µm; 95% CI: –1.01 to –0.07; P=0.03) and when known glaucoma was excluded from the analysis (b=–0.62 µm; 95% CI: –1.11 to –0.13; P=0.01) (7). In the EPIC-Norfolk Eye Study, no association between systolic BP (SBP) and RNFL thickness was reported (8). TES found a negative association between SBP and both RNFL (b=–0.07 µm/10 mmHg; 95% CI: –0.10 to –0.05; P=0.001) and GC-IPL thickness (b=–0.11 µm/10 mmHg; 95% CI: –0.18 to –0.03; P=0.004), in the cross-sectional, but not in the longitudinal, analysis. In addition, a sex-specific U-shaped association was observed: women with SBP and diastolic BP (DBP) below the 10th percentile of the respective distributions (n=88) were found to have thinner RNFL, compared with women whose SBP and DBP values deviated no further than 1 SD from the mean (n=1,000) (d=–1.97 µm; 95% CI: –3.37 to –0.56; P=0.006) (9). This is in line with a previous similar finding from a Dutch population, in which the same definitions of low (n=31) and normal BP (n=21) were used (d=2.6 µm; P=0.002) (16). Last, the multiethnic study of American minorities also reported an association between AH and RNFL thinning (b=–0.62 µm; 95% CI: –1.21 to –0.04; P=0.04) (10).

When considering the role of AH, the following should be highlighted. Again, while most evidence points towards a detrimental effect of AH on the RGCs, scarcity of longitudinal data, differences in genetic background, and AH control standards or adherence complicate any attempt to interpret the results. In addition, it is difficult to disentangle the actual effect of AH on the RNFL, due to the potentially confounding effect of certain classes of antihypertensive medication on the RGCs (17). Some of the aforementioned studies also report a U-shaped association between BP and quantitative RGC metrics. Indeed, both high and low BP can theoretically lead to ischemic insult to the RGCs, the former due to endothelial damage and arteriolar stiffening, the latter owing to exhaustion of the autoregulatory reserve, with subsequent inability to maintain an adequate blood supply (18). This pertains especially to normal tension glaucoma, a subtype of

glaucoma characterized by IOP within normal limits, whose pathophysiology is believed to involve perfusion instability and vascular dysregulation. Last, all significant associations observed in these population studies are, once again, of small effect size, thus not directly translational to clinical practice.

## Metabolic syndrome and glaucoma

Although loosely considered as secondary risk factors, the exact role of each metabolic syndrome component in the pathogenesis of glaucoma has not been fully disentangled yet. With regards to obesity and dyslipidemia, a recent meta-analysis of 18 studies (over 2.7 million subjects in total) reported that dyslipidemia was associated with higher odds for POAG (OR =1.37; 95% CI: 1.16–1.61), albeit with significant heterogeneity (P<0.001; $I^2$=97%). A very small IOP increase in dyslipidemic patients was reported in the same meta-analysis (0.5 mmHg; 95% CI: 0.2–0.8), again with significant heterogeneity (P<0.001; $I^2$=82%) (19). Although recent Mendelian randomization studies suggest a causal relationship between obesity and glaucoma, it is unlikely that such a small increase in IOP can explain the 37% increase in glaucoma risk (20). An alternative explanation could be an increase in retinal venous pressure with concomitant decrease in perfusion pressure. A higher BMI has also been associated with reduced retinal oxygen delivery and extraction in healthy subjects. This could suggest a state of inflammation and oxidative stress, predisposing to glaucomatous damage (21).

A meta-analysis of 47 studies (over 2.9 million subjects in total) reported that diabetes was also associated with higher relative risk (RR) for POAG (RR =1.48; 95% CI: 1.29–1.71), albeit, again, with significant heterogeneity (P<0.001; $I^2$=82%). A very small IOP increase in diabetic patients was also noted (0.2 mmHg; 95% CI: 0.1–0.3), with significant heterogeneity, once again (P<0.001; $I^2$=73%). Recent Mendelian randomization studies suggest a causal relationship between glycemic traits POAG, but such a small increase in IOP cannot explain the 48% increase in RR, alone (22). Indeed, vascular mechanisms involving endothelial dysfunction and concomitant reduction in vascular autoregulatory capacity are thought to be implicated in the relationship between diabetes and POAG.

A meta-analysis of 60 studies calculated an increased pooled RR for POAG (RR =1.16; 95% CI: 1.05–1.28), with modest heterogeneity (P<0.001; $I^2$=35%) in patients with AH. A small IOP increase in hypertensive patients was noted (0.26 mmHg per 10 mmHg SBP increase; 95% CI: 0.23–0.28), with also modest heterogeneity (P<0.001; $I^2$=31%) (23). A recent Mendelian randomization study in a European population did not seem to support a causal linear relationship between AH and POAG (24). However, as already stated, clinical studies have shown that low BP, both naturally manifesting or following antihypertensive treatment, may also exacerbate glaucomatous damage, especially when occurring during nighttime (25).

## Conclusions

The pathophysiological interplay between metabolic syndrome and RGC health remains vastly elusive, owing to the complexity of the associations and the scarcity of longitudinal data. Obesity and dyslipidemia may negatively affect the RGCs, but the effect is likely incremental and the exact relationship may be confounded by anthropometric parameters. Diabetes and AH also appear to have a negative incremental effect on the RGCs, but this likely varies with age, ethnicity, and with overall glycemic or BP control. Caution should be taken, however, since aggressive treatment of AH is potentially even more harmful to the RGCs. While the reported associations are mostly of epidemiological, rather than of clinical, value, clinicians should still be alert about potential confounding risk factors, especially with regards to glaucoma management.

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appropriately investigated and resolved.



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