Invited Commentary

The Association of Systemic Medication and Disease With Intraocular Pressure

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Ho and colleagues[1] studied the cross-sectional associations between common systemic medication use and intraocular pressure (IOP) in the Singapore Epidemiology of Eye Diseases (SEED) study of a population-based cohort. Examining associations with systemic medications is of interest for 2 main reasons. First, understanding such associations may guide our management of patients with glaucoma who are receiving treatment for systemic comorbidities. Second, unexpected associations may point to previously unknown biological mechanisms underlying the regulation of IOP, which may in turn lead to new treatments.

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In their report, Ho and colleagues state that "participants taking systemic β-blockers had lower IOPs. Conversely, the use of systemic ACEIs [angiotensin-converting enzyme inhibitors], ARBs [angiotensin receptor blockers], statins, and sulfonylureas was associated with higher IOP."[1] The finding of lower IOP in people taking oral β-blockers was expected, given the extensive laboratory and clinic-based literature, and on a population level, this replicates a previous report on participants of the European Prospective Investigation Into Cancer (EPIC)-Norfolk Eye Study.[2] The EPIC study examined the relationship between IOP in participants using ACEIs, ARBs, statins, and sulfonylureas but did not find a significant association toward either higher or lower readings. Comparing the details of the analytical methods and results in EPIC and SEED data, one can see differences and similarities.

Both EPIC and SEED analyses carried out multiple statistical tests. The SEED study examined the association between IOP and 22 different classes of drugs. Especially given the exploratory nature of the study, it would be prudent to adjust the threshold for statistical significance to reduce the possibility of false-positive chance findings. For example, a Bonferroni adjustment for 22 statistical tests brings the threshold for statistical significance at the 5% level to $P < .002$. In the EPIC-Norfolk Eye Study, 95% CIs were used to quantify the precision of the effect size. In the SEED study, the probability of all the effects falls within the range where a chance finding cannot be discounted, once one considers the potential impact of multiple statistical testing (ACEIs, $P = .01$; ARBs, $P = .03$; statins, $P = .03$; sulfonylureas, $P = .02$), and 95% CIs were not applied. Considering the Singapore data in isolation in a probabilistic analysis, the scientific case for the putative association must be seen as unproven. If one were to take a Bayesian approach, or to meta-analyze EPIC and SEED data, the results may be different.

While the EPIC data contrasts with the results from the SEED study, pointing to no association between IOP and either ACEIs or ARBs, and a lower IOP in those using statins (−0.31 mm Hg [95% CI, −0.51 to −0.12]; $P = .002$), both the EPIC-Norfolk Eye Study and the SEED study did identify a trend toward higher IOP in people using sulfonylureas (0.67 mm Hg in the EPIC-Norfolk Eye Study [$P = .03$] and 0.34 mm Hg in the SEED study [$P = .02$]). Questions therefore arise regarding the potential explanation(s) for such an association. The Rotterdam Eye Study reported an IOP that was 0.31 mm Hg (95% CI, 0.12-0.50 mm Hg) higher in persons with diabetes than in persons without diabetes.[3] On the basis that the simplest explanation is probably the right one, the association between sulfonylurea use and higher IOP is most plausibly explained by drug use being a marker of diabetes status and its associated phenotype.

The relationship between diabetes, IOP, and glaucoma risk has puzzled ophthalmologists for decades.[4] The association between diabetes and higher IOP seems beyond question. However, clinic-based studies reporting a higher prevalence of glaucoma among persons with diabetes are now widely regarded as the result of ascertainment bias. Multiple longitudinal studies show no increased risk of primary open-angle glaucoma for persons with diabetes.[4] It has been suggested that diabetes may actually be protective against the effects of increased IOP by acting to decrease the risk of glaucoma.[4,5] There are indeed good reasons why this may be true.[4] However, an equally plausible explanation is that measurement error is at least partially responsible for the puzzling coexistence of increased IOP and no increased risk of primary open-angle glaucoma. It is known that the eyes of persons with diabetes have more collagen cross-linking as a result of higher concentrations of advanced glycation end products,[6] therefore resulting in mechanically stiffer corneas.

In a recent analysis of IOP in a very large cohort of predominantly white participants from the UK Biobank, a modified air-pulse tonometer (Ocular Response Analyzer; Reichert Technologies) was used to examine IOP measures calibrated to match the "industry standard" Goldmann applanation tonometer (ie, the Goldmann-correlated IOP [IOPg]), and these IOP measures were compared with those adjusted for the effects of variation in corneal biomechanical properties (ie, corneal-compensated IOP [IOPcc]). Among 110 573 people, it was noted that IOPg measures were 0.41 mm Hg (95% CI, 0.30-0.52 mm Hg) higher among those who self-reported that they were diabetic ($P < .001$) but that the IOPcc measures were no different between persons with diabetes and persons without diabetes (−0.05 mm Hg [95% CI, −0.15 to 0.05 mm Hg]; $P = .38$).[7] Of note, there is a similarity in the effect sizes observed in EPIC and SEED participants taking sulfonylureas (0.67 mm Hg in the EPIC-Norfolk Eye Study and 0.34 mm Hg in the SEED study) and the IOPg difference between those with and those without diabetes in the UK Biobank cohort (0.41 mm Hg).

Taken in the broader context, this offers an argument that the true IOP in persons with diabetes is probably little different from that of the population without diabetes.

This mean difference in IOP between those with and those without diabetes is relatively small on an individual level, but when one considers that the percentage of people with diabetes in different countries is high and increasing rapidly (10.5% of all adults in Singapore, 7.4% in the United Kingdom, and 12.3% in the United States), such an IOP measurement error may influence decisions to treat increased IOP in many people. This reiterates the message that IOP alone is a poor tool for identifying whether an individual has glaucoma, and therefore detection of this important cause of preventable blindness requires a careful assessment of all relevant risk factors, an expert examination of the optic disc, and an assessment of the visual field.

ARTICLE INFORMATION

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