Preventing Glaucoma in a High-Risk Population

Impact and Observations of the Ocular Hypertension Treatment Study

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The Ocular Hypertension Treatment Study (OHTS) was designed to determine the effect of lowering intraocular pressure (IOP) on the conversion from ocular hypertension to identifiable glaucomatous damage in a high-risk population, namely, patients with ocular hypertension (OHTN). Ocular hypertension was defined as an IOP greater than 22 mm Hg. Before the OHTS, some investigators had found that patients with elevated IOPs but no other stigmata of glaucoma developed glaucoma at an annual rate of approximately 2%. However, the value of lowering IOP for patients with OHTN remained unknown.

After an average of 5 years of follow-up, the OHTS found that IOP lowering of approximately 20% decreased the prevalence of glaucoma from 9.5% in the observation group to 4% in the treatment group. These findings clarified the natural history of OHTN and validated the protective effect of lowering IOP.

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Unexpectedly, perhaps the most important impact of the OHTS on routine clinical practice was to highlight the importance of central corneal thickness (CCT). In the OHTS, eyes with a CCT of less than 555 µm were at greater risk for the development of disease progression, independent of the effect of CCT on IOP measurement, as determined by multivariable analysis. Measurement of CCT enhances our ability to identify subpopulations that are at increased risk and to identify those that have a lower risk. Before the OHTS, CCT was rarely measured; now its measurement has become virtually standard practice for the evaluation and management of individuals suspected of having glaucoma and patients with established glaucoma. With the widespread use of corneal pachymetry, patients with thick central corneas are more likely to be spared prophylactic treatment despite elevated IOP. Measurement of CCT allows ophthalmologists to estimate the “true” pressure within the eye and thus establish an appropriate target IOP. However, it is not general practice to convert the Goldmann applanation tonometry measurements based on CCT because the many conversion formulas are not in agreement.

It is recommended that CCT be stratified into average, thin, and thick. Future research may help us specifically define the numerical boundaries that separate these groups. The prophylactic treatment of the subgroup of persons with OHTN who were at higher risk, as found by OHTS, was determined to be cost-effective in a Markov modeling of a Blue Cross/Blue Shield insurer database during a 5-year period. However, treating all OHTN was not considered to be cost-effective.

The OHTS inspired numerous avenues of research. Although it is unlikely that the thickness of the cornea has a direct effect on the pathophysiologic processes, there may be a correlation between CCT and disease susceptibility or modifying variables, such as structural stability of the lamina cribrosa or size of the optic canal. The OHTS renewed interest in the science of measuring IOP, which stimulated the development of alternative tonometers, such as dynamic contour tonometry, and increased the interest in corneal biomechanics. Before publication of the OHTS in 2002, a simple MEDLINE search performed August 8, 2008, with the keyword phrases corneal hysteresis and corneal elasticity revealed approximately 59 citations inclusive of the years 1955 through 2002, a rate of approximately 1.3 per year, with the primary areas of focus being radial keratotomy and keratoconus and some interest relating to tonometry. After 2002, there were approximately 91 citations, a rate of approximately 15.1 per year; most studies focused on IOP measurement, with some interest attributable to corneal collagen cross-linking to decrease of ectasia from corneal surgery or keratoconus.

The OHTS raised some interesting questions about the traditional risk factors for development of primary open-angle glaucoma (POAG) from OHTN. Before the mid-1990s, diabetes mellitus was generally accepted as a risk factor for glaucoma. Several studies, such as the Baltimore Eye Survey, Barbados Eye Study, Melbourne Visual Impairment Project Study, and Proyecto Vision and Eye Research, concluded that diabetes did not confer an increased risk for disease progression. In addition, subsequent to the OHTS, a prospective cohort study from the Rotterdam Study found that diabetes was not a risk for incident cases of glaucoma. However, in the OHTS, diabetes was found to confer a protective effect. It is probable that this surprising finding resulted from a bias in the study design. The OHTS excluded individuals who had evidence of diabetic retinopathy. This exclusion was understandable given the desire to eliminate the chance
of these changes skewing the study results. However, by excluding individuals with diabetic retinopathy, only patients with minimal diabetic disease were included, which would prevent the investigation from estimating the true impact of diabetes. The effect of diabetes on the progression of disease remains highly controversial because several large population studies, such as the Blue Mountain Eye Study, the Rotterdam Study (cross-sectional), the Beaver Dam Eye Study, and the Framingham Eye Study, found that diabetes was positively associated with the development of POAG.13-16

Interestingly, a family history of glaucoma did not increase the risk of glaucomatous progression in the OHTS despite a later finding that CCT is highly heritable.3 The OHTS also enrolled a larger number of persons of African descent (approximately 25%) compared with previous randomized controlled trials in glaucoma. Self-identified African American ethnicity, which has long been held as a strong risk factor for the development of glaucoma, was significant only in the univariable but not in the multivariable analysis.3 Persons of African descent typically have thinner corneas than do persons of European or Asian descent, which is true in children and adults.18-21 The multivariable analysis controlled for age, IOP, pattern standard deviation, vertical cup-disc ratio, and CCT,3 which suggests that ethnicity could have been a surrogate marker for CCT in previous epidemiologic studies. However, in the Barbados Eye Study, which had a high enrollment of persons of African descent (93%), thinner CCT was a risk factor for incident open-angle glaucoma.22

There were numerous instructive observations from the OHTS. The treatment group of the OHTS had a modest therapeutic target of 20% lowering of IOP. However, approximately 50% of patients in the treatment group required more than 1 medication to achieve their target IOP. Physicians and patients should be aware that IOP lowering may require numerous medications, particularly when greater than 20% lowering is required.

Another interesting observation was that patients in the treatment arm of the OHTS had a slightly higher rate of cataract extraction that narrowly missed statistical significance (6.4% vs 4.3%; *P* = .06). The rate of cataract surgery is an indirect measure of functional cataract significance but is not a direct measurement of cataract growth. The Early Manifest Glaucoma Trial, which scored lens opacification with the Lens Opacities Classification System II, found medication treatment to be associated with increasing nuclear opacification (*P* = .002).23

The patients with OHTN were destined to progress to identifiable POAG early in the disease course. In approximately half of the patients whose disease progressed, the progression was measured by optic nerve criteria established through the meticulous examination of optic nerve photographs. This observation highlights the importance of anatomical monitoring in early disease. With all the available technologies for structural imaging, the findings of the OHTS emphasize the importance and impact of diligent clinical examination and the use of simple optic nerve head photography. A subsequent ancillary study24 of the OHTS population, the Confocal Scanning Laser Ophthalmoscopy Ancillary Study, found several baseline measurements of optic disc topography to be associated with the development of POAG. However, the ability of confocal scanning laser ophthalmoscopy to determine progression in advance of optic nerve head photography or visual field testing is still under study.

Finally, the OHTS database was subsequently used, along with a separate group of patients in the Diagnostic Innovations in Glaucoma Study, to develop a single formula (ie, risk calculator) that attempted to synthesize the numerous risk factors for the conversion from OHTN to detectable POAG.25 Before this attempt, one had to try to integrate all of the risk factors from various studies to estimate the risk of an individual patient developing glaucoma. Further refinements will be needed as more information from other studies and longer-term follow-up becomes available, but this first attempt was a major step.

In summary, the OHTS accomplished its primary objectives of determining the natural history of OHTN, measuring the effect of prophylactic IOP lowering, and identifying a new risk factor for the conversion from OHTN to POAG. The OHTS has had a significant and positive effect on our ability to care for our patients.

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REFERENCES


Visualization of Retinal Emboli With High-Resolution Optical Coherence Tomography

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Two patients with retinal arterial emboli in the superior arcade seen on combined infrared scanning laser ophthalmoscopy (A and B) and high-resolution spectral-domain optical coherence tomography (C and D). Emboli are hyperreflective, intra-arterial structures with an either round (C) or flat crystalline-type (D) configuration.