Chapter

Progression from Ocular Hypertension into Glaucoma

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Abstract

Ocular hypertension (OHT) is characterized by raised intraocular pressure (IOP) >21 mmHg without any visual field (functional) or optic nerve (structural) defect featuring glaucoma. Raised IOP is a major risk factor of glaucoma and a proportion of eyes with OHT progresses into primary open angle glaucoma. Glaucoma is a debilitating disease with potential for blindness if left untreated and associated reduction in the quality of life of the affected individual. It is challenging for the clinicians to decide whether an OHT will progress into glaucoma or not based on the risk factor model of the Ocular hypertension treatment study. Moreover, the question whether only IOP or a myriad of factors like central corneal thickness, baseline IOP, visual field, family history of glaucoma, ocular biomechanics are all important in determining the progression is yet to be answered. The rate of progression is also important and needs analysis for further discussion. Summarizing the landmark studies on ocular hypertension and glaucoma to date are imperative in this regard. This chapter presents the overview of OHT and its possible etiology and pathophysiology, risk factors, clinical tests evaluating OHT eyes and elaborates on the progression of OHT to glaucoma over time in relation to the treatment.

Keywords: Ocular hypertension, pathophysiology, risk factors, progression, treatment

1. Introduction

Elevated intraocular pressure (IOP) is an important and the only clinically modifiable risk factor of glaucomatous optic neuropathy [1–4]. Clinically, ocular hypertension (OHT) is most widely defined as raised IOP of > 21 [5] or ≥24 [6] mm Hg in eyes without detectable glaucomatous visual field (VF), optic nerve (ON) or retinal nerve fiber layer (RNFL) damage [6, 7]. It may be also defined as IOP in the highest 97.5% percentile for the population without having optic disc or visual field damage [8]. The prevalence of OHT worldwide varies between 0.32-12.2% [9–15].

Ocular hypertensives have been studied widely through several clinic and population-based studies. The two earliest prospective studies are done by Quigley et al [2] and Georgopoulos et al [16] on large cohort of OHT patients. The first one is the follow-up of 647 OHT patients with IOP >21 mm Hg for 6.2 years. VF testing using Goldmann perimeter (static & kinetic) was performed yearly once [2]. The other study was on 345 untreated patients with OHT (IOP≥21 mm Hg) for a mean duration of 7.3 (6-8) years. VF testing was done every 6-10 months using Humphrey VF analyzer 30-2 program [16].

Ocular hypertension treatment study (OHTS) is the largest multicenter randomized trial involving 1636 OHT participants (aged 40-80 years, IOP 24-32 mm Hg) randomized to either ocular hypotensive drug or to stay under observation for a follow up period of 7.5 years. They were followed up with Humphrey VF 30-2 every 6 months and stereoscopic optic disc photographs every 12 months. Treatment goal was IOP reduction by 20% or more and an IOP of ≤24 mm Hg. The average reduction of IOP achieved with medication was 18.4% which is equivalent to 4.6 mm Hg. In the second phase of the study, the two groups of medication and observation was treated with IOP lowering drugs for another 5.5 years (total 13 years), creating an early treatment and delayed treatment groups [6, 7, 17].

Most population-based studies have shown 9.5-17.4% of OHT eyes develop primary open angle glaucoma (POAG) without treatment over 5 years [6, 17, 18]. Around 1.5-10.5% of these untreated OHT eyes stand at a risk of going blind over the next 15 years [19]. Even after treatment, 4.4% of OHT eyes develop POAG [17] while 0.3-2.4% eyes still carry the risk of becoming blind [19]. Hence, OHT poses a significant socio-economic impact with potential to debilitate the quality of life (QoL) of the diagnosed person once the disease starts progressing [20–24].

2. Pathophysiology

Lamina cribrosa (LC) is a sieve-like structure, which creates a perforation in the sclera through which the axons of the retinal ganglion cells (RGC) exit the eye as optic nerve fibers. The lamina is the weakest point in the wall of the eye. IOP is believed to cause mechanical stress and strain on the LC at the posterior structures of the eye [25]. This results in the compression, deformation and remodeling of the LC at the optic nerve head (ONH) along with axonal damage and blockade of RGC axonal transport (both orthograde and retrograde) to the lateral geniculate nucleus (LGN) [26–28]. It is followed by apoptotic degeneration and death of RGC of the retina and the optic nerve causing vision loss [29].

In experimental glaucoma, disruption of axonal transport causes the collections of vesicles and disorganization of microtubules and neurofilaments in the prelaminar and postlaminar regions [29]. Postmortem of human eyes with glaucoma also revealed these ultrastructural changes in the optic nerve fibers [25]. It was shown that the pressure gradient between the intraocular pressure and cerebral spinal fluid pressure at the lamina cribrosa might be influential in maintaining blood flow in the optic nerve head [30]. When the pressure gradient is increased, the axonal transport would be disrupted, leading to retinal ganglion cell damage. In fact, the degree of RGC death is related to the level and duration of intraocular pressure elevation [29].

This strain also initiates a cascade of molecular and neurotransmitter changes in the surrounding cells of the retina and optic nerve (like astrocytes, microglia, horizontal and amacrine cells, etc.) which alters the microcirculation and remodels the extracellular matrix [29]. Further atrophy and death of the target relay neurons occurs in the magnocellular and parvocellular LGN [28].

The intraocular pressure is a function between the production of aqueous humor from the ciliary processes of the ciliary body and its outflow through the trabecular meshwork (TMW) via schlemm's canal (conventional pathway) and the uveoscleral pathway via ciliary muscle/choroid/sclera (unconventional pathway) [29, 31]. There is an increased resistance found in the aqueous humor outflow through the TM lead conventional pathway in OHT eyes [29, 32]. Thus, resulting in an increase in the IOP, which causes the mechanical stress and strain on the posterior structure of the eye as described.

The average IOP which results from a balance between the normal production and outflow of aqueous humor, which is around 14-15 mm Hg [31, 33]. Although, it is almost impossible to define what is a normal or safe IOP as all individual eyes are uniquely susceptible to the damage caused by IOP. Eyes do not develop any glaucomatous damage in spite of relatively high IOP, whereas, others get damaged even under normal or even relatively low IOP [34, 35]. The result of genetic predisposition and risk factors working alone or their interactions along with the biomechanical properties of the ONH and the scleral connective tissue are hypothesized to account for the susceptibility of individuals under high, normal or low IOP [26].

Secondary damage may occur consequential to RGC death due to the release of glutamate and glycine from the injured neurons leading to excitotoxic damage [36, 37]. Production of nitric oxide may result in oxidative damage to the RGCs and their axons [38–42]. Tissue ischemia-hypoxia is another implicated factor related to glaucomatous optic neuropathy [43, 44]. Reduced ocular perfusion pressure, which is dependent on the systolic and diastolic blood pressure is also found to be associated with higher incidence of OAG [45–47]. Other causes are vascular insufficiency and autonomic dysfunction of the ONH [48–51].

3. Risk factors

3.1 Age

Age is major factor positively associated with the IOP [52]. The Los Angeles Latino Eye Study found higher prevalence of OHT among older Latinos than in younger Latinos ($P < 0.0001$) [53]. Latinos aged ≥80 years had a 3-times higher prevalence than the younger ones (40-49 years) [10]. The OHTS [6] and European Glaucoma Prevention Study (EGPS) [54] found older age (per decade) to have higher risk of progressing from OHT into POAG (hazard ratio (HR) 1.22, $P < 0.05$ and 1.32, $P < 0.05$ respectively). Similarly, a 6 year follow up of urban Australian patients with POAG & OHT to show a significant association of age with the prevalence of POAG [55] and Malmo¨ Ocular Hypertension Study (MOHS) [56] also found older age (per year) as a predictive factor (HR 1.32, $P < 0.05$ and 1.05, $P = 0.034$) of developing POAG among OHT patients in their multivariate analysis.

3.2 Intraocular pressure

IOP is the strongest risk factor associated with glaucoma such that it is regarded as causality. The dose-response relationship has been well documented and demonstrated in several prevalence and longitudinal studies [7, 57–59]. OHTS demonstrated that 23% reduction in the IOP can decrease the incidence of POAG by 60% [7]. Similarly, the Melbourne Visual Impairment Project estimated that for every 1 mm Hg, the risk for glaucoma increased by 10% [60]. Also, the Early manifest Glaucoma Trial (EMGT) and the Collaborative Normal Tension Glaucoma Study (CNTGS) reported an IOP reduction of 25% and greater than 30% can lower the risk of progression by 33% and 50%, respectively, compared to those with no treatment [61, 62]. The Advanced Glaucoma Intervention Study (AGIS) also reported a reduction of IOP to be associated with stable visual fields [57]. A retrospective cohort analysis of 230 OHT patients over 5 years revealed that higher peak IOP is a risk factor for developing POAG in the multivariate analysis. Both the peak IOP and the mean IOP in the progressed group was higher than in the stable group ($P < 0.01$) [63]. IOP per mmHg presented with HR of 1.14 ($P = 0.047$) for developing POAG among OHT eyes in MOHS [56].

3.3 Central corneal thickness

OHTS confirmed thinner central corneal thickness (CCT) to be associated with greater risk of conversion into POAG from OHT [6]. The risk increased by 71% for every 40 μm decrease in the CCT (Multivariate HR 1.71, $P < 0.05$). Similarly, the EGPS found lower CCT by 40 μm to have higher risk (HR 1.32, $P = 0.018$) of POAG [54]. Eyes with thickness ≤555 μm had 3 times increased risk of developing POAG than those with CCT >580 μm [6]. This was probably because thicker cornea has an actual (true) IOP which is lesser than the measured IOP. Conversely, thinner cornea has a true IOP which is higher than measured IOP. Thus, eyes with thicker cornea stand at a risk of getting misdiagnosed as OHT. However, we do not know whether the corneal thickness is associated with factors affecting susceptibility to glaucoma or not.

3.4 Corneal parameters and intraocular pressure and

Corneal properties such as thickness, astigmatism, curvature, hysteresis and biomechanics poses a challenge in measuring the true IOP [64–66]. The Goldmann applanation tonometer (GAT) is known to falsely elevate IOP in thick cornea and falsely reduce IOP in thin corneas [67, 68]. The IOP values measured using CorVis ST is shown to remain almost unaffected by corneal parameters like its thickness and topography through a wide range of IOPs. CorVis ST IOPs were validated on ex-vivo human donor eyes [69, 70]. Corneal characteristics are believed to be strong confounding factors in the measurement of true IOP [70].

3.5 Race

In Phase 2 of OHTS, POAG developed more commonly among African-Americans in the univariate analysis but loses its significance on adding vertical cup to disc ratio (VCDR) and CCT into the multivariate model [6, 17]. However, with similar baseline IOP, follow up IOP and treatment, African Americans have higher risk of developing POAG. This suggests that black race is not associated with an increased risk of glaucoma progression. However, the higher prevalence of other risk factors of glaucoma is present in black individuals such as thinner central corneal thickness (CCT), higher IOP, larger VCDR than their white counterparts [71–73]. Self-reported black race was also identified as an independent risk factor of developing optic disc hemorrhage after 13 years of follow up in OHTS [74].

3.6 Gender

Although males with OHT presented with a higher risk of POAG in the univariate analysis of OHTS (OR 1.87, $P<0.05$), it was not significant in the multivariate model [6]. However, other studies on OHT & POAG patients found male sex to have higher odds of having POAG than females (OR 1.9, $P <0.01$) [55].

3.7 Family history

OHTS failed to find any association of OHT progression with family history of glaucoma [6]. On the other hand, Landers et al studied 301 OHT and 438 POAG patients and reported family history of glaucoma to be a risk factor of having POAG (Odds ratio 1.6, $P < 0.01$) [55]. Similarly, an earlier study on 345 OHT patients revealed that out of 31.6% with family history of glaucoma, 55% developed POAG ($P < 0.001$), which shows family history (heredity) as an important factor in the development of glaucoma [16].

3.8 Myopia

OHTS have found no association between myopia and POAG [6]. However, earlier studies involving patients with OHT and myopia were found to develop glaucoma more than those without myopia [75, 76]. Landers et al. studied patients with POAG (n = 438) and OHT (n = 301) with SAP for a duration of 6 years and reported that myopic patients (SE ≤ -1 D) with OHT have 1.5 times higher risk of developing POAG [55]. Georgopoulos et al. studied 345 untreated OHT with SAP over a period of 7.3 years and found axial myopia ($0.001 < P < 0.01$) to be a risk factor for the development of glaucoma [16]. Similarly, the Casteldaccia Eye Study on 44 OHT/POAG (IOP ≥ 24 mmHg) and 220 controls (IOP ≤ 20 mm Hg) found myopia to be associated with increased (multivariate OR 5.56) of OHT/POAG [77].

Quigley et al. followed 647 OHT patients (40% under treatment) with refractive errors in the range between +12 and -12 D for a period of 6.2 years with Goldmann kinetic perimeter. They showed that there was no association between refractive error and visual field progression [2].

Similarly, the Malmo¨ Ocular Hypertension Study randomized 90 OHT patients to topical timolol or placebo and observed every 3 months for 10 years to conclude that myopia have no influence on the visual field progression. In their cohort, 35% of the myopes progressed compared to the 54% of non-myopes, and there was no significant association between refractive error and VF loss in OHT patients [56].

3.9 Optic disc hemorrhage

Optic disc hemorrhage (ODH) in OHT eyes was associated with a 3.7 times higher risk of developing into POAG ($P < 0.001$) in multivariate model which included the baseline factors predictive of POAG. The incidence of POAG in eyes with and without ODH were 13.6% and 5.2% respectively after 8 years of follow up of OHTS [78]. European Glaucoma Prevention Study (EGPS) also established ODH as an independent risk factor of POAG with HR of 1.97 [79]. After the end of the 13 years follow of OHTS, it was further confirmed in the multivariate analysis that ODH has a 2.6-fold increased risk of converting to POAG ($P < 0.0001$) [74].

4. Visual field testing

Standard automated white-on-white perimetry (SAP) is the most extensively investigated tool for assessment of visual field defects in glaucoma. In SAP, visual sensitivities at pre-defined locations of the retina are measured and compared with age-corrected normative values to detect locations of abnormal visual field sensitivity. SAP employs white stimuli on a white background to quantify visual sensitivity [80]. Visual field parameters including the mean deviation (MD), pattern standard deviation (PSD) and visual field index (VFI) [81] are global indices for measurement of average visual sensitivity and function of an eye. MD is calculated by weighting and averaging the differences of sensitivity thresholds for all the tested points between a subject's thresholds and the normative values. A negative MD indicates overall depression in visual sensitivity. PSD is an index indicating the uniformity of visual field sensitivity. It is determined by comparing the differences between adjacent points. A high PSD value indicates focal visual field loss. A low PSD value, however, can be found in a normal visual field or in an eye with diffuse loss in visual sensitivity. VFI is a percentage of overall visual field sensitivity compared with the normal age-adjusted visual field. VFI has been shown to be less influenced by cataract compared with MD [81]. The severity of glaucomatous

damage can be classified into mild (MD ≥ -6 dB) and moderate-to-advanced (MD <-6 dB) according to the Hodapp-Parrish-Anderson criterion [82]. Glaucoma hemifield test (GHT) [83] is another important parameter incorporating into SAP for glaucoma detection. GHT is calculated by the comparison of five clusters of corresponding test points between the superior and inferior fields. GHT reports the asymmetry of visual field defects in glaucoma. Three categories of visual field are classified by GHT: "within normal limits", "borderline" and "outside normal limits". Yet, a "within normal limits" visual field does not always represent a normal field. Although SAP has been proven to be useful for detection and monitoring of glaucoma [84], early stages of glaucomatous damage may appear as normal in SAP. Because of specific visual function of retinal ganglion cells (RGC) subtypes, selective perimetry can isolate the specific RGCs populations, which was found to detect glaucoma earlier than SAP. There are mainly two types of function-specific perimetries, short-wavelength automated perimetry (SWAP) and frequency doubling technology (FDT). SWAP selectively tests RGCs that target the koniocellular sublayers of the lateral geniculate nucleus by projecting blue stimulus on yellow background. In longitudinal studies, it can detect glaucoma as early as 5 years compared to standard perimetry [85–87]. FDP tests large diameter retinal ganglion cells that target magnocellular layers of the lateral geniculate nucleus and can also detect glaucoma earlier [85, 86, 88]. In a study comparing the diagnostic capability among SAP, SWAP and FDT for detection of early glaucoma (MD > -6 dB), the sensitivities were 46%, 34% and 52% respectively, with specificity ≥97% [89].

In clinical practice, SAP remains the most widely used visual field assessment for diagnosing and monitoring glaucoma. Detecting VF progression (change) over time is difficult and challenging owing to the fact that VF result are largely influenced by several factors [90–95]. Most studies formulated their own criteria to detect VF change with their own merits and demerits [96].

4.1 Visual field testing in ocular hypertensives

Although, optic disc photographs detected most (55%) of the early glaucomatous changes, almost one third had visual field changes as their earliest glaucomatous change in OHTS [7]. Soliman et al evaluated the diagnostic sensitivity of standard automated perimetry (SAP), frequency doubling technology (FDT) perimetry (C-30 full threshold) and short wavelength automated perimetry (SWAP) for the detection of glaucoma damage [97]. The diagnostic performance among FDT perimetry, SWAP and SAP were compared in 42 patients with early to moderate glaucoma, 34 with ocular hypertensives, 22 glaucoma suspects, and 25 normal controls. They found that FDT had similar sensitivity in detecting visual field abnormality compared with SAP but SWAP had a poorer performance in distinguishing the normal group from glaucoma group. The study outcomes were based on measurements of MD, PSD, and percentage of abnormal points. In glaucoma patients, whose baseline SAP was abnormal, FDT perimetry and SAP detected more abnormal points than SWAP. FDT perimetry detected larger defects in ocular hypertension and glaucoma suspects, who showed a normal baseline SAP.

Johnson et al compared automated perimetry and SWAP in a group of ocular hypertension patients and found that SWAP deficits represent early glaucomatous damage and may be related to early changes that occur at the optic nerve head [98].

Bengtsson and Heijl compared the ability of SITA SWAP, full threshold SWAP and SAP (SITA Fast) in patients with ocular hypertension, suspicion of glaucoma (glaucomatous optic disc changes but found no evidence of visual field defect on SITA standard 30-2 SAP) and early manifest glaucoma subjects (repeatable visual

field loss on GHT results) [99]. No significant difference was found between the three algorithms in detecting glaucomatous visual field abnormality. SITA SWAP was able to identify as much visual field loss as the full threshold SWAP but with a considerable reduction of test time.

In OHTS, global and localized rates of VF change were calculated from 780 eyes of 432 OHT patients based on linear regression between MD and time, and between threshold sensitivity values for each test location and time, respectively. It was noted that both the global and localized rates of VF decreased significantly ($P < 0.01$) over a mean of 14 years [100]. Pattern standard deviation or PSD is a weighted standard deviation of the differences between the measured and normal reference visual field at each test location. A high value represents irregularity which can be both due to focal loss in the VF or variability in the patient's responses. Hence, the use of PSD in OHTS has been criticized as it is highly variable and may add a source of error for the baseline as well as the follow up VF measurements [101].

5. Risk factors of visual field progression in OHT

Elevation of IOP has been consistently demonstrated in major clinical trials as a key risk factor for both the development and progression of glaucoma. Baseline IOP, average IOP during follow-up, and fluctuation of IOP has all been reported to be associated with glaucomatous visual field deterioration [6, 102]. Five baseline factors namely, older age, higher IOP, thinner central corneal thickness, larger VCDR and higher visual field pattern standard deviation (PSD) had greater risk of conversion from OHT to POAG [6, 17]. This model was reconfirmed and validated by two independent study population of the EGPS and Diagnostic Innovations in Glaucoma Study (DIGS) [103, 104]. Disc hemorrhage is another important risk factor of visual field progression in ocular hypertension and glaucoma patients [59, 79, 105]. The role of central cornea thickness in glaucoma progression is controversial. EMGT suggests an increased risk of progression in patients with a thinner CCT [106, 107]. Central corneal thickness is a known risk factors of visual field progression in patients with ocular hypertension with 70% increase in risk with every 40μm decrease in corneal thickness [6]. However, as shown in other studies, the association of CCT with visual field progression may not be significant [108, 109].

Other potential risk factors of visual field progression in glaucoma include age, bilaterality, exfoliation, lower systolic perfusion pressure and blood pressure [110–112].

6. Assessment of visual field (functional) progression in OHT

6.1 Trend-based analysis

Trend-based analysis has been used to detect localized and global loss in visual field. MD and visual field index (VFI) are global indices that have been used to estimate the overall rate of visual field progression. The pointwise linear regression (PLR) was first introduced to evaluate visual field progression by Fitzke et al. where the luminance sensitivity of every location from the entire visual field within a series of examination against time was analyzed. PLR has been shown to have a good agreement with Humphrey STATPAC-2 (glaucoma change probability analysis) in separating progressive from stable retinal locations (Kappa = 0.62) [113].

In OHTS, the global and localized VF change rates of 780 eyes from 432 OHT patients over a period of 13 years were calculated based on linear regression between MD and time, and between threshold sensitivity values for each test location and time, respectively. The significant decrease of both the global (MD) and localized rates of VF was recorded ($P < 0.01$). The predetermined criteria of -0.5 dB/year were met in 18.1% eyes. The rate of VF progression before and after the initiation of treatment was -0.23 vs. -0.06 dB/year [100]. The mean rate of change of MD was -0.08 ± 0.20, -0.26 ± 0.36 and -0.05 ± 0.14 dB/year for all, POAG and non-POAG eyes in OHTS ($P < 0.001$) [96].

6.2 Event-based analysis

The pattern deviation map and the total deviation map have been used to detect visual field progression in clinical practice and in glaucoma clinical trials. In the Early Manifest Glaucoma Trial (EMGT), visual field progression, measured by event-based analysis, was the primary outcome measurement of the study. The frequency of visual field progression was compared in 255 early glaucoma patients with and without treatment (treated with trabeculoplasty and betaxolol hydrochloride eye drops). To determine visual field progression, the follow-up visual fields were compared with the average of 2 baseline visual fields in the same eye using glaucoma change probability maps (GCPMs). GCPMs detects significant visual sensitivity worsening at $P < 0.05$ at each of 76 test point locations in the visual field. The EMGT uses pattern deviation GCPMs, rather than the standard total deviation GCPMs, to limit the impact of generalized loss in visual sensitivity secondary to cataract. Definite EMGT visual field progression was defined as at least 3 test points showing significant progression, as compared with the baseline, at the same locations on 2 consecutive GCPMs [62, 114]. The EMGT criteria have been incorporated into the Humphrey Field Analyzer Guided Progression Analysis (GPA, Carl Zeiss Meditec, Dubin, CA). The EMGT criteria have been reported to identify progression earlier than the visual field progression criteria used in AGIS and Collaborative Initial Glaucoma Treatment Study (CIGTS) [84].

7. Assessment of structural progression in OHT

HRT I was used in the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to OHTS which included 865 eyes from 438 participants with ocular hypertension. Forty-one eyes from 36 participants developed POAG based on confirmed visual field defect or optic disc glaucomatous change with a median follow-up time of 48.4 months. Several baseline topographic optic disc measurements taken by HRT I were significantly associated with the development of POAG in both univariate and multivariate analyses, including cup-disc area ratio, mean cup depth, mean height contour, cup volume, reference plane height, and smaller rim area, rim area to disc area, and rim volume. In addition, the classification "outside normal limit" by Moorfields regression analysis (MRA) was also associated with POAG development. It was suggested that HRT I was useful in glaucoma prediction and can be used in glaucoma progression monitoring [115]. The same research group further compared the performance between the baseline glaucoma probability score (GPS) and MRA on predictive ability of conversion from OHT to POAG. Sixty-four eyes of 50 OHT subjects converted to glaucoma based on repeatable visual field defect or optic disc change with a median follow-up time of 72.3 months. In a multivariate analysis, "outside normal limits" global and sectoral baseline GPS showed significant association with the development of POAG with HR ranging from 2.92

to 3.70. In addition, baseline MRA parameters also showed significant association with POAG development with HR ranging from 2.41 to 11.03. It was concluded that both GPS and MRA showed similar performance in predicting the conversion of glaucoma from OHT subjects [116].

In the study by Strouthidis et al on 198 OHT and 21 normal subjects, rim area (RA) progression was calculated with linear regression of sectoral RA/time, defined as slope>1%/year; visual field progression was calculated by PLR of sensitivity/time. The specificities of RA were estimated from 88.1% to 90.5% with the less-stringent criteria, which were as high as the specificities of visual filed progression (85.7% to 95.4%) when standard criteria were used, indicating that both VF and HRT RA trend analysis had relative high specificities for glaucoma progression detection [117]. Although rim area has been shown to be useful for evaluating glaucoma progression, the agreement between rim area progression and visual field progression was often poor [118].

Event-based analysis is also useful for evaluation of rim area progression. In the study by Fayers et al, rim area change was determined using the rim area repeatability coefficient. The specificities were between 76.2% and 100% using different criteria to define rim area progression in 21 normal subjects. One hundred ninety-eight ocular hypertensive subjects were enrolled, 16.2%-45.4% of them were identified to have rim area progression based on different criteria with event-based analysis and 12% showed rim area progression based on trend-based analysis. To evaluate rim area progression, event-based analysis showed a higher progression detection rate than trend-based analysis [119].

GPS has also been used to evaluate glaucoma optic disc progression. Examining the linear regression analysis between GPS and time in 198 OHT subjects, Strouthidis et al showed that 25 subjects (12.6%) progressed by GPS with a significant negative slope ($P<0.05$); 11 of them (5.6%) also showed progression by VF with PLR analysis [120]. Twenty-six subjects (13.1%) had visual field progression alone. The specificity of GPS for glaucoma progression ranged from 95.2% to 96.8%. The conclusion is that the global GPS progression algorithm performs at least as well as previously described rim area-based HRT progression analysis [120]. Higher baseline GPS has been shown to be a risk factor for glaucoma progression in the study by Alencar et al. Two hundred and twenty-three patients with suspected glaucoma were included and followed up for an average of 63.3 months. Fifty-four (24.2%) eyes converted to glaucoma based on repeatable visual field defects and/or optic disc deterioration. Both higher values of global GPS and subjective stereophotograph assessment (larger cup-disc ratio and glaucomatous grading) were predictive of conversion, the adjusted HRs were 1.31 for global GPS, 1.34 for CDR, and 2.34 for abnormal grading, respectively. GPS performed as well as subjective assessment of optic disc in predicting glaucoma progression [121].

8. Features of optic nerve head progression

Using serial optic disc photographs of 259 patients with elevated IOP followed over 15 years, Pederson et al showed that progressive enlargement of the optic cup was commonly the first sign of glaucoma progression [122]. Tuulonen et al detected equal numbers of glaucomatous eyes with diffuse and localized enlargement of optic disc cup in 61 patients with ocular hypertension [123]. In the study by Odberg et al, progressive optic disc cupping occurred most frequently in the superotemporal or inferotemporal quadrants [124]. Lloyd et al examined serial optic disc photographs of 336 eyes of 168 patients with ocular hypertension or early glaucoma [125]. Optic disc progression was defined as: new or increased neuroretinal rim (NRR)

narrowing (2 or more clock hours), notching (1 clock hour or less of narrowing of the NRR), optic disc excavation (undermining of the NRR or disc margin), or development of nerve fiber layer defect. Ninety two of 336 eyes (27.4%) showed optic disc progression after a median of 6.1 years of follow-up. Among those with progression, excavation occurred most commonly (89% of eyes), followed by rim narrowing (54% of eyes) and notching (16%). The inferotemporal quadrant of optic nerve head was the most common location for glaucoma progression [125].

Expansion in the size of peripapillary atrophy was related to glaucoma progression and conversion from ocular hypertension to glaucoma [126, 127].

Another important sign relevant to glaucoma assessment is peripapillary atrophy (PPA). The α zone PPA is located peripherally and characterized by irregular hypopigmentation and hyperpigmentation in the retinal pigment epithelium whereas β zone PPA is close to the optic disc border and characterized by a complete loss of retinal pigment epithelium [128]. Both normal subjects and glaucoma patients can develop α zone and β zone atrophy but the PPA, especially β zone PPA, is larger and more common in glaucoma patients [129]. PPA has been shown to be highly correlated to glaucomatous change [129] and its expansion is also related to glaucoma progression and conversion from ocular hypertension to glaucoma [126].

9. Features of optic nerve head changes

ONH cupping can be due to a combination of NRR loss, lamina cribrosa deformation and prelaminar surface tissue loss. Localized NRR loss can be observed as narrowing or notching of the rim, which is most frequently found in the inferotemporal and supero-temporal sectors of the optic disc [25, 130]. Progressive enlargement of the optic cup is an important sign of glaucoma progression, as shown in a study examining serial optic disc photographs in 259 patients with elevated IOP followed over 15 years [122]. Tuulonen et al studied 61 patients with ocular hypertension and reported an equal number of eyes with diffuse and localized progressive enlargement of the optic disc cup in eyes developed glaucoma over the follow up period of 10 years [123]. Odberg et al reported the supero-temporal and infero-temporal quadrants as the most frequent locations of progressive optic disc cupping [124]. Lloyd et al studied 336 eyes of 168 patients with ocular hypertension or early glaucoma for a median of 6.1 years of follow-up. They examined serial optic disc photographs and showed that for the 92 eyes (27.4%) showing optic disc progression, optic disc excavation occurred most commonly (89% of eyes), followed by rim narrowing (54% of eyes) and notching (16%). The inferotemporal quadrant of optic nerve head was the most common location for glaucoma progression [125]. In OHTS, 69 eyes had optic nerve damage alone without visual field changes. This included 55% of patients reaching the study endpoint [7]. Airaksinen et al [131] followed up 75 OHT patients for 5-15 (mean 10) years using a computerized planimeter and found a decrease in the rim area among 57% of OHT patients. Loss of RA per year was 0.47% and 2.75% among stable and progressing OHT respectively. The loss of RA was linear in half of the patients (49%), with rest as episodic (22%) and curvilinear (29%) [131].

However, it should be remembered that both OHT and EGPS used serial optic disc stereophotographs to measure the vertical CDR which is known to have high intra- and inter-observer variability among clinicians [132]. Moreover, the current optic disc imaging and measurement techniques namely HRT & OCT neither correlate well with stereophotographs and nor with the disc margin (which coincides with the Bruch's membrane opening or BMO) [133–135]. This disagreement in the VCDR measurement might give rise to variable result of OHT progression into

POAG [136]. Although, BM is a stable ONH structure and is less affected by age or increasing IOP, eyes with high myopia often have poorly visible BMO and overhanging BMO due to the BM shift [137–139].

10. Progression of ocular hypertension

Overall, 90% to 95% of patients with ocular hypertension did not go on to develop Glaucoma. After 5 years, 4.4% and 9.5% developed POAG under the medication and observation group respectively in phase 1 of OHTS. Use of medication was protective against POAG with a HR of 0.40 (95% Confidence Interval (CI): 0.27-0.59, P < 0.0001) compared to those under observation. The treatment had significant effect on both the optic disc and visual field changes. Early treatment of OHT reduces the 5-year incidence of POAG by 60% [6, 17].

In the 2nd phase of OHTS, the two groups of medication and observation were both treated with IOP lowering drugs for another 5.5 years (total 13 years), creating an early treatment and delayed treatment groups. There is a linear risk of OHT converting to POAG over 15 years. Cumulative proportion of study participants developing POAG was 0.16 vs 0.22 (P = 0.009) in early treatment vs delayed treatment groups. The median time to develop POAG was delayed in the early treatment groups than the delayed ones (8.7 vs 6 years) [17, 74, 140].

Starting treatment after the appearance of early signs of POAG do not have any significant negative effect on visual field loss over next 5 years, given the patients follow up regularly. Clinicians need to assess both the structural and functional parameters in OHT eyes to determine disease status and progression [6, 7, 17].

DIGS also found the predictive model suggested by OHTS to be useful to assess the 5-year risk of developing POAG among their independent population of 126 OHT patients [104]. DIGS also found long term IOP fluctuation not associated with risk of developing POAG in untreated OHT subjects (multivariate HR 1.08, P = 0.62). However, mean IOP, i.e., the level of IOP during follow up was significantly associated (HR 1.20 per 1mm higher, P = 0.005) [141]. Similarly, MOHS with 10-17 years of follow up of their OHT patients also found mean IOP level (HR 1.21, P = 0.005) to be significantly associated with increased risk of POAG, but not IOP fluctuation (P = 0.49) [142].

11. Treatment

OHT and POAG treatments are mainly focused at using topical prostaglandin analogs to increase the uveoscleral outflow pathway [143, 144]. Prostaglandin analogs are quite potent IOP lowering drugs which are well tolerated without much side effects and require only one dose at night to cover the nighttime peak IOP hours [144]. However, some patients still require adjunctive therapy with other drugs as topical beta-adrenergic antagonists (suppresses aqueous production), alpha-adrenergic agonists (suppresses aqueous production + increases uveoscleral outflow), and carbonic anhydrase inhibitors (suppresses aqueous production) [143, 144].

Clinical trials on topical hypotensive drops showed Latanoprostene bunod 0.024% to have a significantly better IOP lowering effect compared to either latanoprost 0.005% or timolol 0.5% over 1 year among European, North American and Japanese patients with OHT/POAG [145, 146]. The side effect profiles were similar among the medications [144].

A multicenter randomized controlled trial (Laser in Glaucoma and Ocular Hypertension trial or LiGHT) compared ocular hypotensive drops (588 eyes) vs

selective laser trabeculoplasty (SLT) (590 eyes) in newly diagnosed OHT and POAG patients. This RCT was unique in its novel approach of including QOL as an outcome measure and defining the target IOP, which was specific for each individual based on their disease severity and risk of vision loss. Moreover, target IOP was adjustable based on IOP control and disease control which resembles common clinical practice more than a fixed algorithm [147, 148]. It was found that eyes treated with medicine first progressed faster compared to the laser first eyes. Total deviation (both pointwise & global) as well as pattern deviation had a greater risk of progression (risk ratio 1.37-1.55, $P < 0.001$) in the medicine first group than the laser [149]. The efficacy between SLT (611 eyes) and topical hypotensive drug (622 eyes) among eyes with OHT and POAG over 3 years were assessed through another randomized controlled trial. They found both SLT and medication to be equally effective in lowering absolute IOP in both OHT and POAG eyes. IOP control without eye drops was achieved in 75% of eyes after 1-2 SLTs [150].

Benefits of early treatment are more in high-risk patients (determined using the five-factor model of age, IOP, CCT, CDR and visual field PSD) than those with low risk. No benefit of early treatment was found for patient in the low-risk group [17].

EGPS failed to find any significant difference in IOP among OHT patients with and without dorzolamide after 5 years. Dorzolamide reduced IOP by 15-22%, whereas, the IOP in placebo group also got reduced by 9-19% ($HR < 1$, $P > 0.05$) [103].

12. Conclusion

There are several risk factors associated with the progression of OHT into glaucoma. Measurement of the true IOP is an important aspect of distinguishing patients with OHT from those with normal IOP and thicker cornea. Patients with OHT must be first evaluated and classified as having high risk or low risk of glaucoma. Only high risk OHT eyes poses a major threat of progressing into glaucoma. However, there are inherent limitations which must be considered while using the five-factor model. A better formulation of the risk assessment technique is warranted for more practical classification of OHT in clinics. Treatment with ocular hypotensive drugs or laser on high-risk patients is an effective way to reduce the risk of OHT eyes progressing into glaucoma.

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