

OPHTHALMIC DOCTORATE

The normal optic nerve variations in an optometric population

Possible ocular and systemic influences

Catherine Collin

2014

Aston University

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**The Normal Optic Nerve Variations in an Optometric
Population: Possible ocular and systemic influences.**

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Doctor of Optometry**

**Aston University
July 2013**

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Synopsis

Early detection of glaucoma relies on a detailed knowledge of how the normal optic nerve (ONH) varies within the population. The purpose of this study focused on two main areas;

1. To explore the optic nerve head appearance in the normal optometric population and compare the south Asian (principally Pakistani) with the European white population, correcting for possible ocular and non-ocular influences in a multiple regression model. The main findings were:

- The optic discs of the South Asian (SA) and White European (WE) populations were not statistically different in size. The SA group possessed discs with increased cupping and thinner neuro-retinal rims (NRR) compared with the WE group. The SA group also demonstrated a more vertically oval shape than the WE population. These differences were significant at the $p < 0.01$ level.
- The upper limits of inter-eye asymmetry were: ≤ 0.2 for cup to disc area ratio, and 3mmHg for intra-ocular pressure (IOP) for both ethnic groups and this did not increase with age. IOP asymmetry did not vary with gender, ethnicity or a family history of glaucoma and was independent of ONH asymmetry. ONH and IOP asymmetry are therefore independent risk factors when screening for glaucoma for both ethnic groups.

2. To investigate the validity of the ISNT rule: inferior > superior > nasal > temporal NRR thickness in the optometric population. The main findings were:

- As disc size increased the disc become rounder and less vertically oval in shape. Vertically oval discs had thicker superior and inferior NRRs and thinner nasal and temporal NRRs compared with rounder disc shapes due to cup shape being independent of disc shape. Vertically oval discs were therefore more likely to obey the ISNT rule than larger rounder discs.
- The ISNT rule has a low adherence in our sample of normal eyes (5.7%). However, by removing the nasal sector to become the IST rule, 74.5% of normal eyes obeyed. SA eyes and female gender were more likely to obey the ISNT rule due to increased disc ovality. The IST rule is independent of disc shape and therefore more suitable for assessing discs from both ethnic backgrounds. Obeying the ISNT rule or IST rule was not related to disc or cup size.

Acknowledgments

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List of Abbreviations

AOREC	Audiology and Optometry Research Ethics Committee
BP	Blood Pressure
CDR	Cup Disc Ratio
CRA	Central Retinal Artery
DDLS	Disc Damage Likelihood Scale
GPS	Glaucoma Probability Score (HRT-III)
HRT	Heidelberg Retinal Tomograph
IOP	Intra Ocular Pressure
IST	Inferior>Superior>Temporal
ISNT	Inferior>Superior>Nasal>Temporal
NCT	Non-Contact Tonometer
NFL	Nerve Fibre Layer
NICE	National Institute for Health and Care Excellence
NRR	Neuro-Retinal Rim
OCT	Ocular Coherence Tomography
OHT	Ocular Hypertension
ONH	Optic Nerve Head
OPP	Ocular Perfusion Pressure
PPA	Peripapillary Atrophy
α -PPA	Alpha-PPA
β -PPA	Beta-PPA
RPE	Retinal Pigment Epithelium
SA	South Asian
UK	United Kingdom
WE	White European
VF	Visual Fields
2D	2- dimensional

3D	3-dimensional
600	60 dioptré
900	90 dioptré

Statement of Authenticity

This thesis is the work of Catherine Collin during a 5 year postgraduate research programme at the School of Life and Health Sciences, Aston University, Birmingham, UK. The study was undertaken in private optometric practice in Accrington, Lancashire, UK. This work has not been presented in any previous application for a degree and all the work was performed by the undersigned. All the figures and photographs are original. The author has no commercial interest in any of the equipment used in this work.

Chapter 1

Introduction

1.1 Background

Glaucoma is an optic neuropathy characterised by a loss of optic nerve fibres resulting in characteristic changes to the optic nerve head (ONH) and visual field loss. It is a potentially blinding disease that affects approximately 2% of the UK population over 40 years of age. The incidence of glaucoma varies between different ethnic populations, it is known to be higher in the Afro-Caribbean population and to a lesser extent the Asian population compared with the white population (Stein et al 2011). For the majority of patients, the disease can be controlled or slowed, but once damage has occurred it cannot be reversed. Early diagnosis is therefore important, as early glaucoma is asymptomatic and most cases are picked up during routine screening with an optometrist. There have been many studies looking at the optic nerve structure in the normal population. More recent studies have used newer technologies, in particular the ocular coherence tomograph (OCT) and Heidelberg retinal tomograph (HRT) instruments. There appears to be general agreement in the positive relationship between cup and disc size. The Blue Mountains study in particular found a significant relationship, concluding that for each 1mm increase in size, the cup size increased by 0.270 (Healey et al 1997). However not all studies agree, an Indian study in 2001 suggested that this relationship may not be as marked as previously thought and disc size could not be used to predict cup size (Sekhar et al 2001). The UK population has a significant Asian population, and any differences in the optic nerve head structure between these two groups are important for glaucoma screening; nevertheless, this is an area that has attracted little investigation and will therefore be addressed in this study.

Glaucoma results in death of the optic nerve fibres and is often but not always, associated with an increase in intra-ocular pressure (IOP); the role of blood flow to the optic nerve head is also thought to play a role in glaucomatous damage. The nerve fibre loss occurring in glaucoma creates a visual field defect that reflects the area of nerve fibre layer (NFL) affected. Detection of early loss can be especially difficult due to the large variation in the appearance of the ONH. Discs can be large or small, cupped, flat or tilted. In addition, patients often visit different optometrists, often with no available notes to compare with. The cup to disc ratio (CDR) is the most commonly recorded feature of the optic disc in optometric records. Newer technologies such as OCT or HRT allow in depth assessment and examination of the ONH and NFL and now play a major role in the diagnosis and long-term management of ONH pathology (Samarawickrama et al 2012), although for the mainstay these remain the remit of hospital based practice. For the community based optometrist, direct ophthalmoscopy and indirect ophthalmoscopy using an indirect lens and slit lamp remains the norm. Fundus photography is also becoming increasingly used in optometric practices. Optometrists perform a screening role in

glaucoma detection and see many thousands of normal patients each year. In the absence of any obvious glaucomatous signs, a normal IOP and visual fields, a disc with a large cup is dismissed as physiological. The poor specificity of detecting glaucoma solely by disc assessment is well known, highlighting the difficulty in detecting early disease. Many practitioners, with constraints on time and resources, target visual field assessment only for those patients they consider at risk; invariably this includes those with a family history, raised IOP or deeply cupped discs. Nevertheless, this practice could possibly result in overlooking some very early glaucoma cases. The neuro-retinal rim thickness is considered to be thickest in the order: inferior, superior, nasal and temporal, known as the ISNT rule, emphasis is frequently placed on whether a disc obeys the ISNT rule, although evidence based studies for the validity of this rule are lacking.

1.2 The Optic Nerve Head: Anatomy and physiology

A detailed knowledge of the anatomy and physiology of the optic nerve head is crucial when screening the normal population for glaucoma.

1.2.1 Optic Nerve Head Anatomy

The optic nerve head, also known as the optic "disc" comprises of the most anterior part of the optic nerve as viewed from inside the eye and lies 3mm from the macula. The disc itself is pinkish in colour and measures approximately 1.5mm in diameter and is vertically oval in shape. The disc diameter depends on the diameter of the choriocleral canal at the level of Bruch's membrane. The sclera becomes perforated at the ONH called the lamina cribrosa which allows the nerve fibres to exit the eye together with the retinal vessels. The total optic nerve tissue volume is not thought to vary wildly in normal eyes; this is supported by studies which have found increased cupping in larger optic discs (Hsu et al 2012).

In the frontal plane, the disc anatomy is important in imaging and recording. The disc size is commonly taken to be between the inner edges of the scleral ring where it meets the retinal pigment epithelium (RPE) (Meyer et al 2001) and is seen as a thin white band. Inside this band, is the neural retinal rim (NRR) comprising of neural tissue which appears pinkish in colour. The cup is the central depression in the ONH devoid of neural tissue and its size and presence varies hugely between individuals. In some eyes, outside the scleral ring there is a retraction of the RPE causing an area of bared sclera to be seen, this is known as beta-zone peripapillary atrophy (β -PPA) and is thought to be a risk factor for glaucoma as it is commonly found in these patients. A pigmented area of peripapillary atrophy due to increased pigmentation can also sometimes be seen, known as alpha-zone (α -PPA) but is thought to be less significant. The presence of PPA can make the identification of the disc rim difficult which in turn can make optic disc measurements

variable. This is a problem both in subjective disc assessment and particularly in objective and computerised disc analysis, it has been reported that the diagnostic capability of the OCT declines with increased PPA (Kim et al 2012). The identification of the optic cup can also be problematic due to the highly variable shape, the cup edge is often the most difficult contour to identify and does not always correspond to colour changes (Bourne [2008]). Some cups have very well defined steep edges that can be easily identified; others have shallower, sloping cups which prove harder to define. Larger discs have a poor diagnostic ability for rim and disc areas but higher improved diagnostic ability for CDR and cup volume (Kim et al 2012), probably by virtue of having larger cups. Identification of the cup edge can be aided by careful observation of the retinal vessels as they dip into the cup and by using stereo cues, see figure 1.1a. Computerised methods of locating the cup and disc require the reference plane of the disc margin to be defined and differences between instruments will affect the measurements obtained. An accurate assessment of the disc and cup edge allows an accurate measurement to be obtained of the NRR area and cup to disc ratio (CDR).

The intra-orbital part of the optic nerve is 25mm long, the optic nerve head itself is 1mm long and comprises of four parts:

1. The superficial nerve fibre layer (NFL)
2. The Pre-laminar layer
3. The laminar region
4. The retro-laminar region

Figure 1.1a: Physiological cupping

Showing normal vessel deviation



Figure 1.1b: Flat disc, or absence

of cupping



The superficial nerve fibre layer

At the optic nerve head, the retinal ganglion cell axons converge and bend into the optic nerve. The fibres are separated from the optic nerve tissue by the astrocyte rich inner limiting membrane of Elsching. In normal optic nerve cupping, this membrane is often thick and called the central meniscus of Kuhnt, as cupping increases, this becomes thinner (Hayreh 2011). The NFL also has a dense capillary network derived from the retinal circulation via the central retinal artery, together with the larger vessels which feed the retina.

The Pre-laminar layer

As the retinal nerve fibres enter the optic nerve head they pass into the pre-laminar layer which mainly comprises of glial and connective tissue, forming the anterior part of the lamina cribrosa. The connective tissue fibres are associated with vessels and are larger than the glial fibres. The glial tissue fibres are flattened cells orientating transverse across the optic nerve head forming a mesh through which the nerve fibres travel, at the disc edge they are attached to the choroid. This border between the tissue of Elsching in the pre-laminar layer and the choriocapillaris in the choroid means that the pre-laminar region of the ONH lacks a blood-optic nerve barrier (Hayreh 2011). The ganglion axons in this region are grouped into bundles surrounded by glial tissue septa prior to entering the lamina cribrosa.

Laminar region

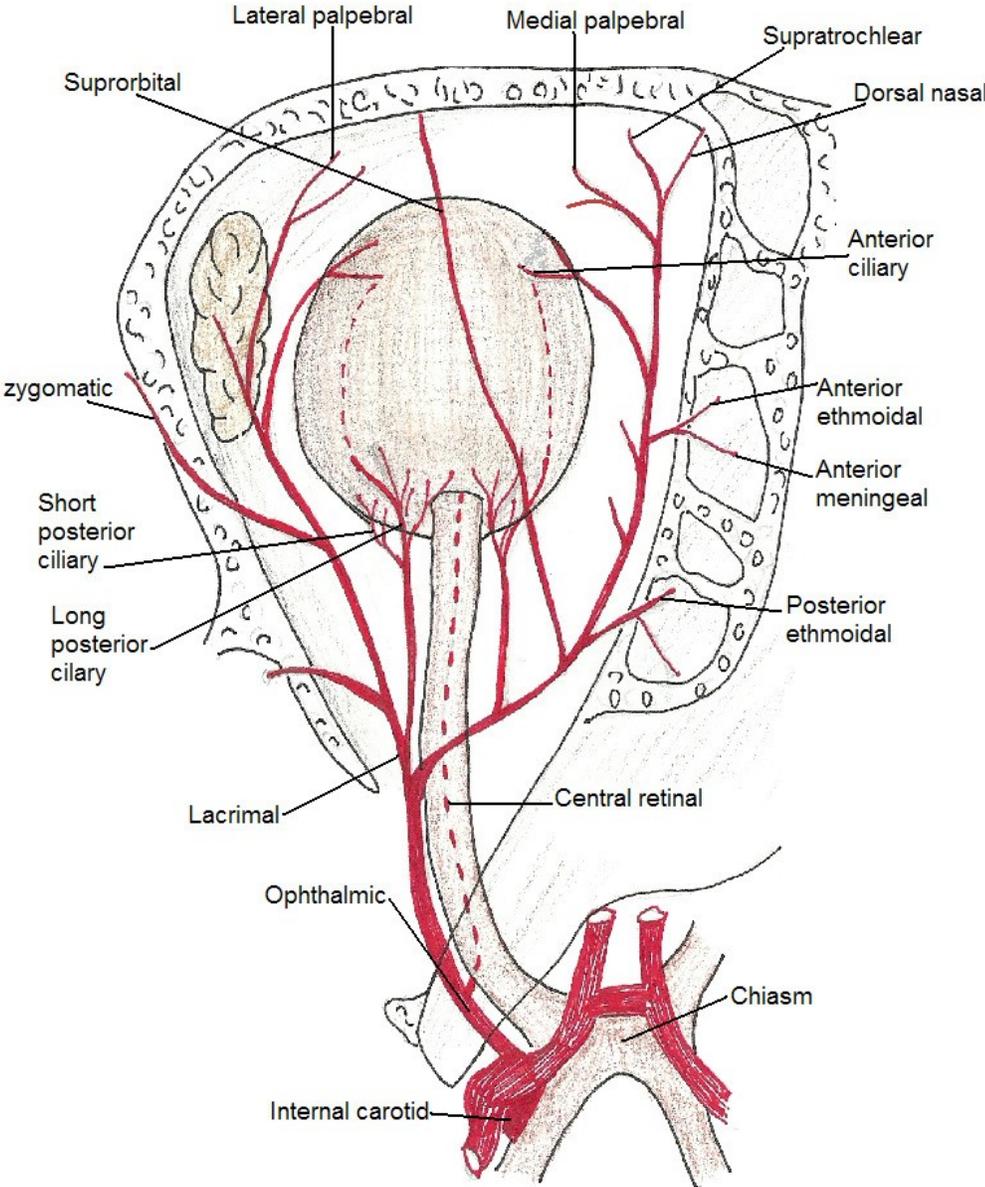
This comprises of the lamina cribrosa which can often be seen on ophthalmoscopy as a paler dimpled area in eyes with cupping. It is comprised of connective tissue fibres and forms a supporting network for the retinal nerve fibres between 146 and 278 μ m thick as they enter the more posterior retro-laminar layer. Between the beams of the lamina cribrosa, the ganglion axons run through and between the specialised fibres (Dai et al 2012). The lamina is continuous with the sclera, however histological samples also suggest that it also inserts into the pia mater (Sigal et al 2010). The lamina cribrosa also forms a barrier between the intraocular space where the pressure is lower, and the higher pressure of the extra-ocular space. This prevents leakage of the aqueous humour into the retrobulbar space (Jonas et al 2003). This pressure gradient across the lamina cribrosa is implicated in glaucoma, increases in IOP cause displacement of the lamina cribrosa and enlargement of the sclera canal (Sigal 2012). An abnormally rigid lamina and sclera will result in lower IOP damage compared to highly elastic tissues.

Retro-laminar region

The retro-laminar region lies posterior to the lamina cribrosa and begins at the point where the retinal ganglion axons become myelinated. The myelinated axons are surrounded by the meninges of the central nervous system (Besharse et al 2010). The astrocytes of the myelination transition zone in this region are the target of raised IOP (Dai et al 2012) and are implicated in the pathogenesis of glaucoma.

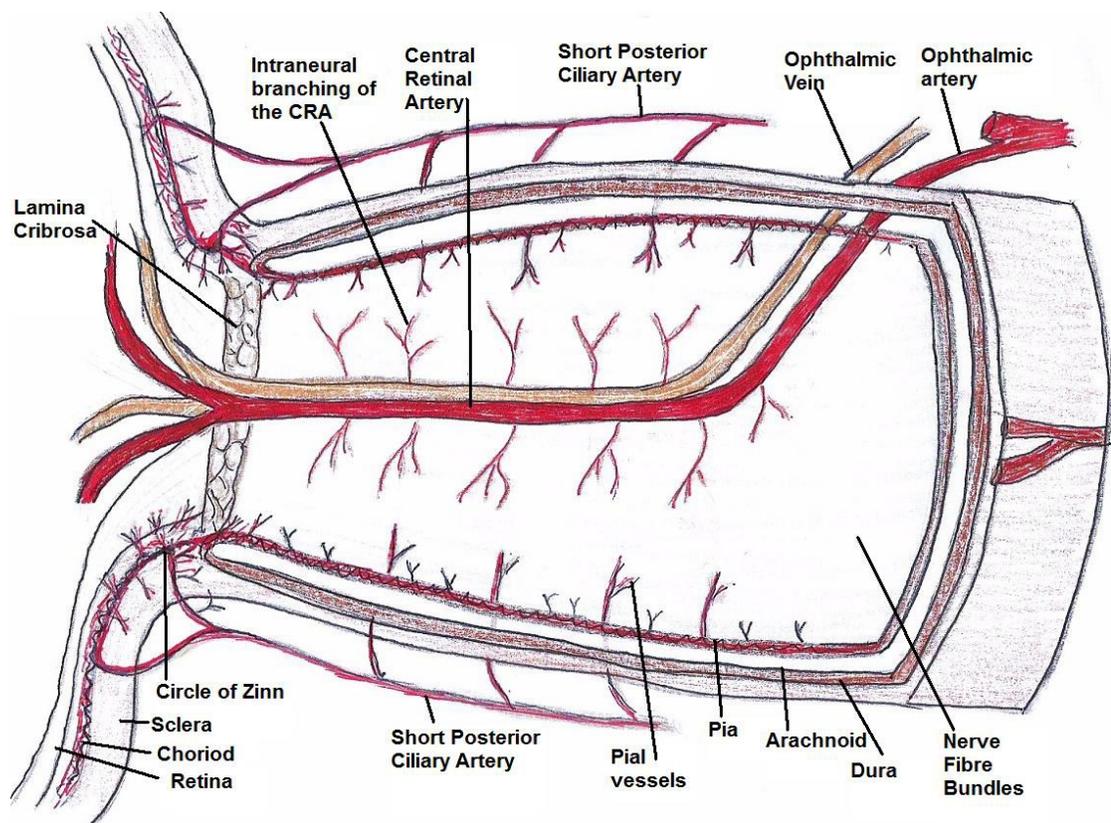
1.2.2 Ocular Vascular Anatomy

Figure 1.2 Blood supply to the orbit:



The eye and orbit receives most of its blood supply from the ophthalmic artery, which is the first branch of the internal carotid artery. The ophthalmic artery enters the orbit through the optic canal, running infero-laterally to the optic nerve in most cases. The ophthalmic artery then runs nasally, anteriorly and superiorly to the optic nerve where branches form the central retinal artery (CRA), posterior ciliary arteries (PCAs) and branches to the extra-ocular muscles. (Besharse 2010). The optic nerve head receives most of its blood supply from the short posterior ciliary arteries. Usually two branches of PCAs divide near the posterior aspect of the globe and divide again to supply the choroid and another to the arterial circle of Zinn-Haller.

Figure 1.3: Optic Nerve Head Blood Supply



- The NFL layer receives its blood supply from the retinal circulation capillary bed supplied from the CRA, in addition, if a cilioretinal artery is present, this also supplies the NFL layer in that sector. The capillaries supplying the NFL are non-fenestrated with tight junctions and originate from the retinal arteriole branches called epipapillary vessels and these in turn, originate in the peripapillary NFL.

(Besharse 2010). There is no direct choroidal circulation contribution to the NFL (Mackenzie et al 2008).

- The pre-laminar layer is supplied by the short posterior ciliary arteries, which travel through the choroid and around the arterial circle of Zinn-Haller. The choroidal circulation itself is not thought to directly contribute the pre-laminar ONH blood supply, although this is difficult to assess.
- The laminar layer is supplied by the short posterior ciliary arteries directly or by the arterial circle of Zinn- Haller. The pre-capillary arterioles perforate the outer aspect of the lamina cribrosa before branching into an interseptal capillary network (Mackenzie 2008). The larger pericapillary arterioles of the choroid occasionally contribute small arterioles to the lamina cribrosa region.
- The retrolaminar region is mainly supplied by the pial arteries, these are centripetal branches derived from the ophthalmic artery entering from the pia.

The borders between the parts of the nerve supplied by different arteries are known as the watershed zones and it has been suggested that they are more susceptible to glaucomatous nerve damage due to reduced vascularity in these areas.

1.2.3 Optic Nerve Head Physiology

- **Intraocular Pressure**

The intraocular pressure (IOP) is the pressure of the fluid within the eye; it depends on the balance between aqueous production and drainage. The upper limit of normal IOP is 21mmHg, which is the mean IOP+2SD as measured in the normal population. This rule was adopted from an original study by Hollows who produced a normal distribution for IOP using a normal population aged 40-75 years (Hollows et al 1966). Today this limit is used by NICE as the upper cut off for normal IOP.

IOP is measured indirectly by applying a force to the cornea and measuring the resistance which is converted to an IOP measurement; this is based on the Imbert-Fick law which states that the pressure is equal to the force per unit area of appplanation for a spherical container, assumed to be infinitely thin, dry and perfectly elastic.

Imbert-Fick law: $IOP = \text{Contact Force} / \text{Area of contact}$

However, the cornea is not infinitely thin and the resistance also depends on the corneal thickness and structural integrity of the tissue. Goldmann tonometry uses an appplanation area of 3.06mm, at this value, the corneal rigidity and tear film opposing forces approximately cancel out giving the IOP measurement. The corneal thickness and rigidity

are assumed a common value in calculating IOP, but will vary between individuals. It is now common practice in ophthalmology to measure the corneal thickness and make an adjustment to the recorded IOP. This is not commonly done by optometrists. Raised IOP does not always indicate glaucoma but is a known risk factor. Patients with normal visual fields and discs are considered to have ocular hypertension (OHT). The decision whether to treat OHT depends on the risk of the patient converting to glaucoma, the patients age and the level of IOP. The neurogenic control of IOP is not well understood. There is some evidence that the non-pigmented ciliary epithelial cells show some noradrenalin activity which may be responsible for at least part of the circadian variation in aqueous production which decreases 50-60% at night (Doshi, 2009). Despite the fall in production, the IOP increases during the night and the melatonin and noradrenalin levels increase.

- **Aqueous production and drainage**

The production of aqueous humour is thought to be a combination of active secretion from the non-pigmented cells of the ciliary body epithelium and leakage of fluid from the blood. Drainage is via two pathways: the trabecular outflow and the uveoscleral outflow. Drainage through the trabecular meshwork forms the main pathway and the rate of flow is dependent on the resistance of the trabecular tissues and the hydrostatic pressure within the eye. Increased resistance of this pathway is known to be a major cause of raised IOP, particularly in the pigmentary glaucomas. The uveoscleral pathway is independent of IOP and forms a minor, fairly constant component of aqueous drainage. The aqueous is absorbed through the vessels of the ciliary body into the periorbital tissues through the scleral wall.

- **Measurement of IOP**

The Goldmann applanation tonometer is regarded as the gold standard for IOP measurement and used by ophthalmologists almost exclusively. There have been several alternative tonometers developed in recent years including the tono-pen, I-care rebound tonometer and the Pascal dynamic contour tonometer. However, in a screening setting, such as an optometric practice, the use of non-contact tonometry (NCT) is more commonly used. The NCT uses a stream of air to applanate the cornea and does not require anaesthesia or physical contact with the cornea. Further details of the NCT are given in the methods section 2.2.3.

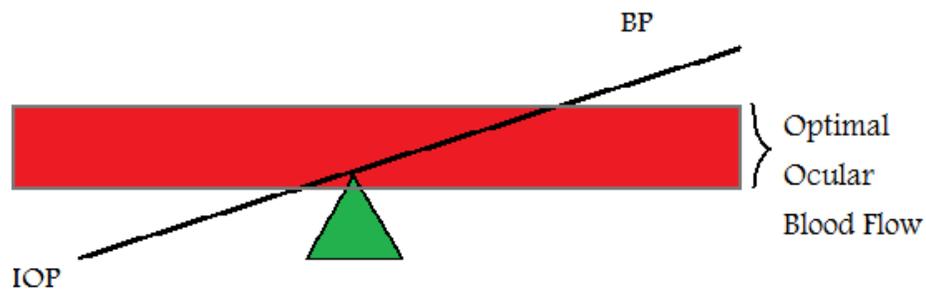
The IOP fluctuates on a diurnal basis and with fluctuations with the arterial pulse. Other factors affecting the IOP measurement include variations in blood pressure, eye rubbing and accommodation. Due to these variations, it is advisable to repeat IOP measurements on more than one occasion and imperative before any referral is made with a suspicion of ocular hypertension. Many local primary care trusts in the U.K now have schemes in place

to refine potential optometric referrals for ocular hypertension. This is in response to the NICE guidelines issued in 2010, which state that all patients with IOP levels over 21mmHg should be referred to an ophthalmologist.

- **Optic Nerve Head Blood Flow**

The optic nerve requires a constant blood flow. This is achieved despite fluctuations in systemic blood flow by auto-regulation by the smooth muscle layer of the arteries. The fluctuation in vascular tone is achieved by a combination of endothelial, myogenic and metabolic factors and by hormones and nerves. The sympathetic nervous system, although controlling blood flow towards the eye, does not influence the ocular circulation. In the normal optic nerve, the ocular blood flow is maintained within tight limits. The blood flow may fall outside these limits if the auto-regulation is abnormal or if either the IOP or systemic BP falls outside the auto-regulatory capacity. Abnormal regulation is implicated in glaucoma, large fluctuations in OPP can cause transient ischemia and reperfusion and result in tissue damage.

Figure 1.4: Illustration of The balance between IOP and BP



- **Ocular perfusion pressure (OPP)**

Optic nerve head blood flow relies on the ocular perfusion pressure divided by the resistance to flow. Blood flow is therefore dependant on three main factors: IOP, BP and vascular resistance. It is known that large increases in systemic blood pressure, increased carotid blood flow and central venous pressure will cause an increase in IOP. Therefore there is a close relationship between ocular blood flow and IOP. The ocular perfusion pressure is the mean arterial pressure minus the venous blood pressure in a vascular bed. The calculation for OPP is given in the methods section: 2.2.5.

1.3 Current methods of assessing the optic nerve head

When discussing the results of this research, and making comparisons with other studies, it is important to note that many recent studies of the ONH utilise modern imaging

systems, an understanding of these techniques is therefore essential. A thorough examination of the optic nerve head is essential to any eye examination, whether optometric or ophthalmic. There has been an influx of new technology designed to both image and analyse the optic nerve head in recent years, although these remain for the majority in hospitals and research units. The methods of recording and analysing the optic nerve head in practice and research will also be discussed, with relevance to glaucoma.

1.3.1 Ophthalmoscopy

Direct ophthalmoscopy is the longest established method of optic disc assessment and is still commonly used in optometric practice. It is a relatively cheap, portable instrument, making it ideal in a domiciliary environment. The direct ophthalmoscope achieves a highly magnified view of the optic disc (15x in an emmetropic eye) making it easier to see small disc haemorrhages and focal loss than some other methods, the field of view is only 10° but a good view can be achieved through small pupils although the image is degraded by media opacities. Studies have found the best discriminators for glaucoma screening using direct ophthalmoscopy to be the vertical and horizontal CDR, the narrowest rim width and the presence of PPA. Both direct and indirect ophthalmoscopy allows visualisation of the disc in true colours and detects the presence or absence of venous pulsation. However, direct ophthalmoscopy is monocular, and the lack of binocular cues such as the margin of the cup can be misinterpreted, often resulting in a larger estimation (Harper 2000), it is also the least useful method in assessing cup depth. The apparent disc size also varies widely due to magnification differences with refraction, making it difficult to judge the actual disc size in clinical practice; this effect is not seen using indirect ophthalmoscopy. Indirect ophthalmoscopy using a hand held lens and slit lamp achieves a less magnified but stereoscopic view of the ONH, the view is also less affected by media opacities. Commonly a 60D lens is used to view the ONH at a working distance of 11mm, giving a magnification of 1.15x, the image is laterally reversed and upside down. The disc size can be measured by adjusting the slit beam to coincide with the disc margin and read off the calibration scale, a correction factor is then applied depending on the indirect lens used. The disc size is very important when judging the significance of the cup and NRR area, with larger discs reportedly having larger cups.

The difficulty in judging the disc size with direct ophthalmoscopy is perhaps why optometrists place such reliance on the cup/disc ratio (CDR) when grading the optic disc. The CDR was first described in 1969 (Armaly 1967) and has since been widely used in optometric practice; however this grading does not consider disc size, notching or focal rim thinning. A newer method of grading the ONH has been suggested, called the disc damage likelihood scale (DDLS) (Hoh et al 2003) This scale describes the disc using a 5

point scale from "definitely normal" through to "definitely abnormal" and aims to describe the disc based on the narrowest radial NRR width and the vertical disc diameter grouped into small, medium and large discs (<1.5mm, 1.5-2mm and >2mm) (Bayer et al 2002). It has been shown that inter and intra-observer agreement for the vertical DDLS is greater than for the CDR using ONH photographs (Spaeth et al 2002), however when studied in vivo, the results were similar (Hoh et al 2003). The DDLS is still not an ideal grading scale, atypical discs prove difficult to grade with both techniques and discs that suffer focal loss followed by later diffuse loss would also not be suitable, as the narrowest radial width will stay the same.

The main disadvantage of both fundus photography and ophthalmoscopy is they provide visualisation of only the surface of the ONH; it is probable that IOP induced deformations and changes occurring in the interior of the ONH are more relevant when considering IOP induced damage (Sigal et al 2009).

ophthalmoscopy and fundus photography however are the mainstay for glaucoma screening and disc monitoring in the general population and are commonly utilised in many high street optometrist practices.

1.3.2 Heidelberg retinal tomography (HRT)

The main application of this instrument is analysis of the ONH. The instrument measures the topography of the ONH but does not differentiate between different retinal layers. There are three generations of this instrument: the HRT-I, II and III. The HRT-II requires the observer to draw a line manually around the disc and the software calculates various parameters including the disc and cup areas, cup/disc area ratio, cup depth, mean NFL thickness and also provides a cup shape measure. The cup shape measure has been suggested as a useful measure in detecting glaucoma, the more positive the value, the more abnormal the cup shape. In the newer HRT-III, a 3D topographical map is produced. The image produced is not a photograph but a colour coded reflectance map.

The HRT-II uses the Moorfields regression analysis in which the ONH is divided into 6 sectors and the NRR area compared with a normative database. A study in 2007 found that subjective grading of ONH photographs agreed better with the Moorfields regression than any other automated analysis (Reus et al 2007). Newer software for the HRT-II and HRT-III uses automated methods of ONH modelling (Swindale et al, 2000) which do not require a contour line, the instrument finds the disc rim where the RPE/ choriocapillaris layer terminates at the lamina cribrosa and is reference plane independent. However, some patients with visual field defects have been classified as normal by the HRT (Shin et al 2008) indicating limitations with the analysis. The most recent HRT-III also incorporates

a mathematical model of the ONH shape in the "glaucoma probability score" (GPS). The GPS also uses a 6 sector analysis of the ONH and produces a score from 1 (low probability of disease) through to a score of 6 (high probability of disease), this is based on the cup size and depth, NRR slope and curvature of the NFL. It is also based on a larger normative database than the Moorfields technique.

Ocular Coherence Tomography (OCT)

In contrast to the HRT, OCT has multiple applications as it can obtain large area transverse and axial measurements of the ONH, macula and retina. Its main uses are in the investigation of macula and optic nerve disease. The OCT is also able to image the microvasculature of the ONH. The Zeiss Stratus OCT provides NFL and optic nerve images and measurements and incorporates software to detect progression. The Zeiss OCT-3 has a fast optic disc scan programme which performs circular scans of 3.4mm around the ONH and measures the NFL in the peripapillary region, an operator is required to position a marker at the centre of the ONH. The programme produces 6 radial line scans through the ONH and gives cross sectional information on cupping and NRR area. The instrument automatically identifies the disc rim, a line is drawn 150µm anterior and parallel to the edge of the RPE/chorocapillaris layer, above this line is defined as NRR, below is defined as the cup. This difference in this reference line can result in differing cup/disc values between OCT and HRT. A study in 2007 found that the OCT produced higher CDR values compared to indirect Ophthalmoscopy, particular for small cups (Arnalich-Montiel et al 2007, again possibly due to this factor. The 2D images obtained can be combined to produce a 3D image of the ONH. Current OCT is unable to penetrate the sclera, deep penetrating OCT is being developed which may provide a method of reaching the lamina cribrosa obscured by the sclera (Sigal et al 2010).

The HRT and OCT are not interchangeable; the HRT tends to give lower measurements than the OCT for all values except cup depth (Seymenoğlu et al 2013). Studies using different instruments cannot therefore be directly compared.

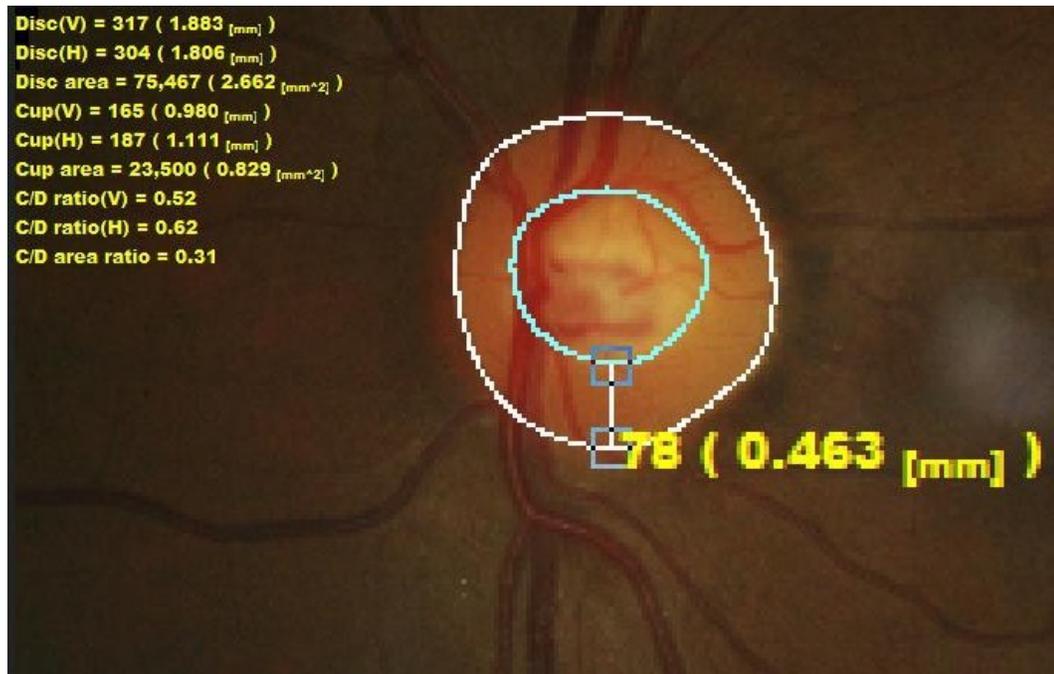
Fundus photography

Photography has been used in ophthalmology for many years and is becoming increasingly used in optometric practices. NICE guidelines recommend that images are taken of a patient at diagnosis as a baseline so further changes can be identified and repeated when a change is seen. This is in contrast to the newer imaging techniques that aim to help in the diagnosis of glaucoma as well as provide baseline data. Digital imaging is now the norm, with good resolution, fast acquisition and transfer of images possible. The images are true to colour and can be enlarged; they can also be viewed in red free to

facilitate the detection and width of NFL defects, a study in 2009 found that 20-40% of NFL defects detected using photography were missed using newer imaging techniques (Windisch et al 2009), although it has been suggested that NFL defects may not correlate with the amount of tissue loss (Townsend et al 2009). Photography is particularly good at detecting disc haemorrhages, a study in 2008 found that clinical examination found only 16% of haemorrhages seen on fundus images (Uhler et al 2008). Fundus photography can be performed with un-dilated pupils in many cases and be performed with minimal training making it suited to screening, as is currently used for diabetic retinopathy screening. Fundus images need to be corrected for magnification in order to measure the size of the ONH and this is specific to the camera. The magnification of the camera is a constant of the camera multiplied by the vergence of the internal eye which can be calculated from the equivalent spherical refraction; other methods use refraction, keratometry and axial length, other factors affecting the magnification include the eccentricity on the fundus and the camera position (Garway-Heath 1998). Telecentric cameras have the anterior focal point of their first lens coincident with the first principal point of the eye; however the observer must accurately focus the eyepieces (Rudnicka et al 1998). These variations make it difficult to compare measurements obtained from different instruments. Stereo images can be produced from stereo pairs that are alternately displayed so that the polarisation state of the liquid crystal alters in phase with the refresh rate of the monitor, the observer then views the monitor using polarised glasses, this technique is used in the "soft imaging system", a Z-screen is another method used by the Cardiff system (Sanfilippo et al 2009).

Planimetry is the method used by fundus camera imaging software to measure optic disc, cup and area size, it is regarded as the gold standard for quantitative evaluation of ONH morphology (Sanfilippo et al 2009). An observer marks around the disc and cup rim using a pointer, the location of the rim is aided by the stereoscopic view, the most effective way is to define certain points on the disc and cup rim where their location is clearer, aided by tracing a path of vessels across the scleral ring and NRR (Harper et al 2000). The software then fits a polynomial curve for the cup and disc (see figure 1.5); this has shown high correlation with 60D slip lamp viewing (Sanfilippo 2009). The disadvantage here is the subjective nature of marking the cup and disc, but this is true for all subjective assessments by ophthalmoscopy, it does allow the observer to assess the disc and detect the presence of PPA, disc haemorrhage and NFL defects if present

Figure 1.5: Planimetry



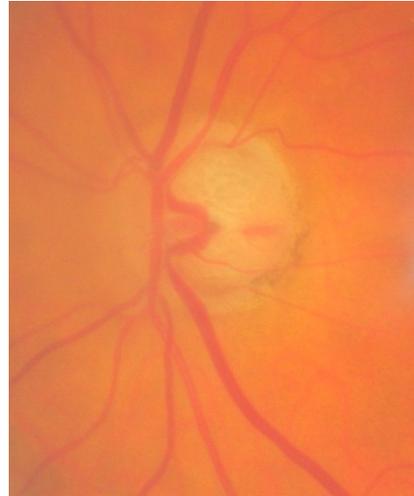
Discs that are difficult to assess such as irregular shapes, tilting or discs with extensive PPA can also be identified and less emphasis placed on the CDR if these structures are not well defined. The Rotterdam study in 1999 found that semi-automated stereo fundus images produce higher CDRs than direct and indirect ophthalmoscopy and tended to overestimate cup sizes in small discs (Wolfs et al 1999).

Automated assessment of the ONH based on 3D reconstructions of stereo photographs has also been developed, the results are comparable to direct observation with the exception of disc and cup areas, the disc area tends to be larger in automated measurements due to PPA, as shown in figure 1.6a. The main aim of fundus camera software is to document the disc and aid the clinician in detecting further progression rather than producing statistical likelihoods of the presence of glaucoma or progression. Photography can be a very useful tool in Optometric practice as it allows the clinician to compare images taken years apart, detecting subtle changes that may otherwise be missed.

Fig 1.6a: normal right eye



fig 1.6b: End stage glaucoma left eye



The photograph of end stage glaucoma in figure 1.6b was taken 8 years after diagnosis, had serial photographs been available, earlier diagnosis may have been possible. Planimetry allows the cup and PPA to be measured on new and old images providing a measure of progression or stability.

1.4 Glaucoma

Introduction

Glaucoma is a group of optic neuropathies causing a loss of the retinal ganglion cell axons; it is commonly but not always associated with raised IOP. There are several types of glaucoma, the commonest being primary open angle glaucoma (POAG). The aetiology of POAG is still not completely understood and the range of intraocular pressure at which damage occurs is highly variable, even accounting for corneal thickness and ocular perfusion pressure. Death of the retinal ganglion cells results in loss of the neural retinal rim tissue and results in an enlargement of the optic cup. Early disease is asymptomatic but can progress to permanent loss of visual field. Early diagnosis is therefore important, patients often present late in the disease or are detected by routine screening

1.4.1 Definition and demographic

“Primary open-angle glaucoma is described distinctly as a multifactorial optic neuropathy that is chronic and progressive with a characteristic acquired loss of optic nerve fibres. Such loss develops in the presence of open anterior chamber angles, characteristic visual field abnormalities, and IOP that is too high for the continued health of the eye” (Bathija et al 1998)

Glaucoma is a major cause of blindness both in the western world and worldwide. It currently affects approximately 2% of the population in the over 40 age group and is the world's second largest cause of blindness after cataract (World Health Organisation 2002). Currently 10% of all blindness registrations in the U.K and over 1 million outpatient appointments each year are due to glaucoma (nice.org.uk 2011).

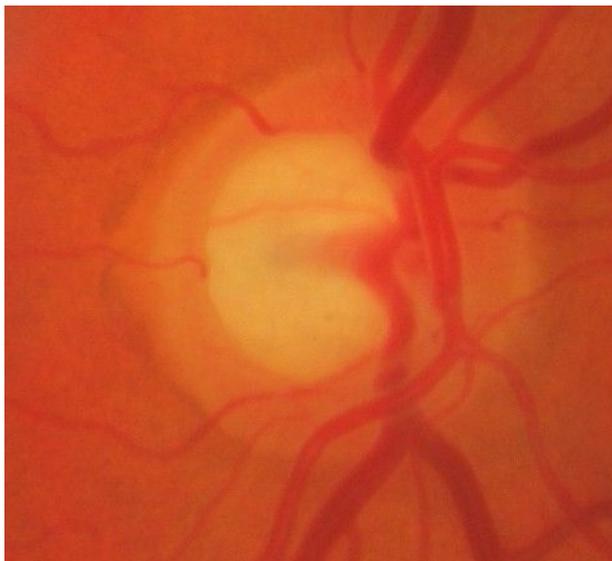
1.4.2 Risk factors

Abnormal IOP is the most important risk factor in glaucoma. Other factors include an immediate family member with the disease, increasing age, and abnormal local and systemic blood circulation. Certain ethnic groups are also known to have a greater incidence of glaucoma. This issue will be discussed in chapter two of the present thesis.

1.4.3 Glaucomatous changes

In glaucoma, loss of the retinal nerve fibres and consequentially the NRR occurs resulting in an enlargement of the cup (fig 1.7). Early loss can be difficult to detect due to the large anatomical variation in the normal disc.

Figure 1.7: Glaucomatous disc



This disc shows an enlargement of the cup together with a loss of small retinal disc vessels and glaucomatous deviation of the temporal vessels dipping under the edge of the cup; this is in contrast with the physiological cupping shown in fig 1.1a. Atrophy is also present at the temporal disc edge.

Often the superior and inferior nerve fibres are lost first resulting in thinning of the NRR and vertical enlargement of the cup, both diffuse

loss and focal notching can occur. Other cues for the development of glaucoma include the presence of disc flame haemorrhages (see figure 1.8), vascular changes, increased beta zone PPA and nerve fibre layer (NFL) defects (Fingeret et al 2005).

Figure 1.8: Flame haemorrhages

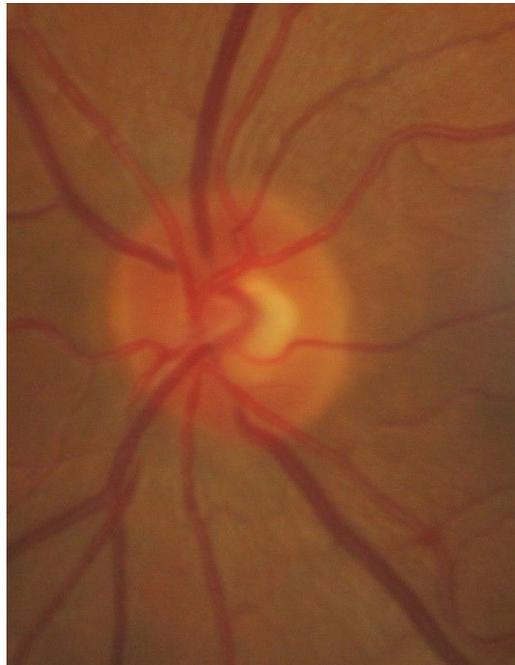
Clinicians are taught to identify signs of Glaucoma such as neural retinal rim (NRR) thinning resulting in increased cupping, absence of the ISNT rule, vertical cupping, bayoneting, the presence of haemorrhage and disc asymmetry between the two eyes. The ISNT rule was first described by Jonas (Jonas et al 1988) and describes the normal NRR as being thicker in the inferior quadrant followed by superior and nasal, and thinnest in the temporal quadrant. This rule has been used for many years to assess a discs likelihood of normality, with glaucomatous discs less likely to obey the rule (Harizman et al 2006), however a recent study has thrown doubt into the rule's validity in describing the normal disc (Iester et al 2011).



Figure 1.9: Individual disc asymmetry in Glaucoma

Right eye

Left eye



Asymmetry of the cupping between eyes is also indicative of glaucoma, see figure 1.9. Normal eyes rarely show a CDR difference greater than 0.2 (Jonas 1988). The lamina

cribrosa was previously thought to be the source of the mechanical damage to the retinal axons caused by pressure damage, but newer studies have suggested the astrocytes within the ONH to play a major role (Dai et al 2012). It is proposed that axonal damage is caused by loss of metabolic support by damaged astrocytes rather than mechanical damage. Nguyen et al 2011 found that these astrocytes express Mac-2, a gene usually expressed in phagocytic cells. Therefore it is possible that the astrocytes undergo pressure induced apoptosis. The vascular theory implicates ischemia as the cause of axonal damage caused by alterations in ONH blood flow; this could explain the damage occurring in normal tension glaucoma and patients who continue to progress despite good IOP control. It is also supported by the connection between vaso-spastic syndrome and glaucoma.

The methods of assessing and recording the optic disc fall into three groups are discussed in section 1.5 and include:

1. Direct assessment of the patient, including direct and indirect ophthalmoscopy with written and descriptive recording.
2. Optic disc photography with planimetry or computerised image analysis.
3. Newer imaging techniques such as optical coherence tomography (OCT) and confocal scanning laser Ophthalmoscopy using the Heidelberg retinal tomograph (HRT).

1.4.4 Current screening methods

The gold standard for ONH assessment remains indirect ophthalmoscopy. Clinical evaluation is based on many ONH features including the size of the disc, NRR, presence of haemorrhage and β -PPA, vascular changes, colour, disc and cup shape and inter-eye differences. Despite the recent advances in imaging, all these factors have yet to be included in the HRT/OCT software. There is currently no gold standard for assessing the CDR or defining the cup and disc border. In addition, the use of different instruments makes direct comparisons in studies difficult. Many studies have been done comparing the HRT and OCT to stereo photographs in the diagnosis of glaucoma. Generally the HRT tends to yield higher CDR's than the OCT and both appear to have a similar diagnostic accuracy in glaucoma screening (Heidelberg engineering.com). The addition of morphometrics should further improve diagnostic accuracy. Morphometry uses the ONH shape, as this information is lost in simple measurements of size or ratios. There are limited population studies on optic disc shape to date and few ways to quantify optic disc and cup shape (Sanfilippo et al 2009). Further longitudinal studies are needed comparing these techniques in the detection of progression.

1.4.5 Current optometric referrals of glaucoma suspects

A glaucoma suspect is identified and referred based on IOP levels, visual fields and optic disc assessments. The patient's age and a positive family history of glaucoma also play a key role in the referral decision. A study in 2010 found that only 2/3 of optometric referrals contained all three tests (Lockwood et al 2010). The implementation of the NICE guidelines has resulted in many primary care trusts developing glaucoma refinement schemes such as repeat IOP testing using Goldmann tonometry by the original optometrist, or referral to a specialist glaucoma optometrist prior to referral to an ophthalmologist. Both options have dramatically reduced referrals to the hospital eye service, a study in 2011 found that after repeat Goldmann tonometry, 76% of patients did not require referral (Parkins al 2011). The emphasis in optometric practice is very often on IOP; visual fields are often performed only when the IOP is high, there is a positive family history or the CDRs are large. Estimation of disc size is rarely done by optometrists. There is a need for a better understanding of the anatomy and variability of the ONH in the normal population to allow optometrists to improve glaucoma detection rates.

Chapter 2

Literature Review

2.1 Ethnic differences

Many studies mainly based in the US have investigated ethnic differences in glaucoma incidence and normal optic nerve appearance, but due to the ethnic mix of the US, these mainly include white and African ethnicities (Marsh et al 2010, Leske et al 1991, Sing 2000). In the UK, the largest ethnic minority is South Asian (SA), principally of Indian and Pakistani origin. Population estimates from the office of national statistics are shown in table 2.1. However some areas of the UK have a much higher proportion of people from a south Asian background than others.

Table 2.1: UK population estimates 2009, (modified from the office of national statistics.gov.uk)

Ethnic Group (UK)	population (1000s)
All Groups	54809.1
White British	45682.1
White Irish	574.2
White Other	1932.6
Caribbean	310.6
African	80.7
Indian	1434.2
Pakistani	1007.4
Bangladeshi	392.2
Chinese	451.5
Other Asian	385.7

Clinicians screening for glaucoma in areas with a high south Asian population will therefore benefit from knowledge of any differences between these two groups, both in the incidence of glaucoma and the normal optic disc topography. The current study was carried out in the Hyndburn area of east Lancashire, with a population comprising of 87.6% white and 11.2% south Asian (Lancashire.gov.uk, 2011 census). To the authors knowledge, this is the first study to directly compare the normal ONH in the south Asian and white optometric population.

2.1.1 Inter-ocular difference in optic disc topographic parameters: inter-ethnic comparison.

Knowledge of normal Inter-ocular differences are important as an early sign of glaucoma can be cup asymmetry. Little is known, however, of how the ONH appearance between right and left eyes of an individual varies in different ethnic groups. Studies investigating inter-ocular differences tend to consider one ethnic group and most have found little clinical difference between right and left eyes (Hwang et al 2012, Gherghel et al 2000,

Mwanza et al 2011, Durukan et al 2004). To the author's knowledge, no study has investigated ethnic inter-ocular differences.

2.1.2 Glaucoma incidence

The African population is reported to suffer a higher incidence of glaucoma than the White population (Leske et al 2009, Tielsch et al 1991); although the White population may show a greater increase in primary open angle glaucoma (POAG) with age (Rudnicka et al 2006). Data on the Asian population with regards to POAG incidence is less well documented. Stein et al (2011) reported POAG prevalence rates of 6.52% for American Asians which was higher than the White population; the authors also reported even higher hazard rates for narrow angle glaucoma and normal tension glaucoma in the Asian population. It is difficult to directly compare studies carried in the Pakistan and India with studies elsewhere due to the differences in study design and the use of different clinicians. The UK is well placed to conduct a multi-ethnic study into glaucoma incidence due to the high south Asian population.

2.1.3 Normal Optic nerve head

Ethnic differences in the appearance of the optic nerve head between subjects of European and African origin are well known. It is well documented that the African/Caribbean population have larger discs and higher CDRs compared with the White population (Sample 2009, Giradin 2007, Girkin 2005, Marsh 2010, Zangwill 2004, Varma 1994). Despite having larger discs, subjects of African origin have been found to have similar NRR areas to the white population (Varma et al 1994); a recent study by Knight et al (2012) found no racial differences in ONH parameters between these groups when corrected for disc area.

The Asian groups form a much smaller proportion of the population in US studies and include subjects from the Far East including China and Japan; the south Asian population forms a much smaller percentage of the US population. Studies into the Asian population have centred on Pakistan and India and do not directly compare with other studies of other ethnicities. It has been suggested that SA population have a larger disc size than WE population (Nangia et al 2008, Mansour et al 1991). Estimates for the mean disc area in the SA population vary: 2.25mm² using HRT (Nangia 2008), 2.63mm² using OCT (Decosta 2005) and 3.37mm² using fundus images (Sekhar 2011). These variations within the same ethnic groups using different instruments in different studies highlight the difficulty in comparing the findings to studies using other ethnic groups.

2.2 The “ISNT” rule

The “ISNT” rule relates to the decrease in NRR thickness in the four sectors of the ONH, being thickest at the Inferior rim, followed by Superior, Nasal and Temporal rims. The ISNT rule is commonly used in optometric practice as a means of assessing the ONH for normality (Jonas, personal communication).

2.2.1 Origins and rationale for use of the rule

The ISNT distribution of NRR thickness was first observed by Jonas et al (1988) and gradually adopted into clinical practice (Jonas, personal communication), to the extent that many optometric record cards include an ISNT assessment as standard. In the original study by Jonas, the average NRR thickness in each sector was reported for 457 eyes. The study did not suggest the use of the ISNT rule and did not state how many individual eyes obey this NRR thickness pattern

2.2.2 The ISNT rule and the normal ONH

Subsequent studies since Jonas’ paper in 1988 have investigated the adherence to the ISNT rule in normal eyes have also had mixed results and vary widely between studies as can be seen in table 2.2. The wide variations are likely to be due to differences in measurement with some studies using planimetry and others using computer aided analysis. In addition there are differences in the authors’ interpretation of the ISNT rule.

Table 2.2 Adherence to ISNT rule (normal eyes): Review of previous studies.

Author	Date	% ISNT obeyed
Larsson	2011	56%
Harizman	2006	67%
Iester	2011	12.44%
Lundmark	2010	80%
Sihota	2008	29%
Pogrenick	2010	39%
Sihota	2007	71%

In the original study by Jonas et al (1988), the optic disc was divided into 4 unequal sectors to mirror the NFL: the superior and inferior sectors covered 90° tilted 13° temporally, with the temporal sector and nasal sectors covering 64° and 116° respectively.

Results for rim area within these sectors and rim thickness were reported. In the original study, the mean NRR thickness were: Inferior: $0.50\text{mm}\pm 0.18$, superior: $0.46\text{mm}\pm 0.18$, nasal: $0.44\text{mm}\pm 0.18$ with the temporal rim standing out clearly as the thinnest ($0.30\text{mm}\pm 0.16$), however these are mean values and it is unclear how many individual eyes followed this pattern. When considering deep and large cupping the NRR thickness differences were minimal apart from the temporal rim (Jonas et al 1988); this also agrees with a study into paediatric cupping which found that larger cups were more likely to violate the rule (Pogrebriak 2010). A subsequent paper by the Jonas found that the superior, inferior and nasal rims did not vary significantly in thickness (Jonas et al 2003). The original paper presented findings of normality; the idea of the ISNT rule in glaucoma screening came later, its origins and its use as a glaucoma screening tool is unclear; which is surprising considering its widespread use today.

Figure 2.1: The four ONH sectors used in

the original paper by Jonas et al (1988)



Some studies have followed Jonas's original sector approach using NRR area (Sihota 2007, Lundmark 2010), and some studies use the NRR thickness (Harizman 2006). Other studies have measured the thickness at the 4 principle meridians or adopted a new approach such as rim area in 10,20,40 or 90° segments (Morgan 2012). It is therefore not surprising that there is disagreement. These differences are further compounded by the location of the nasal cup edge which varies with the position of the retinal trunk, some studies have disregarded the nasal NRR due to these problems but also because the nasal NRR is the last to be affected in early glaucoma. It is also worth noting that although published results may report a statistical difference between NRR thickness in the four sectors, it may not be of clinical significance or detectable by eye. The ISNT rule is used as a quick check by clinicians and needs to be detectable by ophthalmoscopy in a practice setting. Many published papers report either the inferior rim to be the thickest (Jonas et al 1988, Pogrebrinak et al 2009), or similar thicknesses for the inferior, superior

and nasal rim (Jonas et al 2003, Lester et al 2011). An Indian study found the nasal rim to be thicker than the superior rim (Arvind et al 2008), another Indian study found the temporal rim to be significantly thinner than the other sectors, whilst the other three sectors were similar (Jonas 2003). Jonas found that greater vertical disc diameters were associated with higher inferior: temporal ratios and higher superior: temporal ratios (Jonas et al 2003). It has also been found that increased vertical disc diameters are associated with a broken ISNT rule (Lundmark et al 2010), however only the diameter was considered, not the shape.

2.2.3. The ISNT rule and its use in glaucoma screening

Despite its widespread use, subsequent studies have found the effectiveness of the ISNT rule in glaucoma screening to be less useful than previously thought (Hanzman et al 2006, Morgan et al 2012, Sihota et al 2007). It would appear that not enough glaucoma eyes fail the ISNT rule and a significant number of normal eyes also fail to obey the rule, for it to be a useful glaucoma screening tool (Morgan 2012). The inferior: temporal NRR rule and the superior: temporal rule provided the greatest diagnostic power in glaucoma, but was of little clinical value. An Indian study found that the ISNT rule was intact in 71% of normal eyes and 68% of eyes with early glaucoma and concluded that the superior: temporal rim ratio showed the highest predictor for early glaucoma (Sihota 2007)

Chapter 3

Methods

3.1 Recruitment of Subjects

The research participants were recruited from the optometry population as they attended for an eye examination at a high street optometric practice. The study took place in Accrington, Lancashire, a typical small town in North West England. The main ethnic groups for the Hyndburn area of Lancashire are: 87.6% White and 11.2% Asian (Lancashire.gov.uk, 2011 census). Ethical approval was obtained from Aston University's ethics committee and written informed consent was received from all participants prior to enrolling on the study. If the participant was unable to read English, a translator was used. Both the participant and the translator were asked to sign the consent form.

3.1.1 Exclusions

In order to recruit normal adult subjects, free from optic nerve disease, ocular hypertension or potential iatrogenic influences, the following patients were excluded from this study:

- Aged under 16 years. Studies on glaucoma and optic discs often include only the glaucoma screening population ie over 40 years of age. Subjects between 16 and 40 were not excluded in this study to order to investigate the influence of age on the OHN appearance in both ethnic groups and on obeying the ISNT rule.
- Having undergone any form of intra- ocular surgery which could affect the refraction or IOP measurement, such as refractive surgery, cataract surgery or retinal detachment surgery.
- Positive diagnoses of glaucoma or ocular hypertension, as these subjects do not fall into the normal population category.
- Any other optic nerve disease, as this could affect the disc appearance.
- Patients who were referred with a suspicion of glaucoma/ocular hypertension during the visit, these subjects cannot be classified as normal until deemed so by an ophthalmologist.
- Patients who were unable to understand the study or read the information sheet/consent form. These included patients with dementia, reduced responsibility, or limited English in the absence of a translator.
- Patients with a recorded IOP of >21mmHg. Although many subjects with an IOP above 21mmHg may still be normal, under the NICE guidelines, they fall into the ocular hypertension classification and in line with the nice guidelines these patients were referred to an ophthalmologist for further investigation.

3.1.2 Patient information sheet and consent form

A copy of the information sheet and consent form can be found in appendix 2 and 3. The participants were asked to tick their ethnic group on the consent form. Translators were asked to sign the consent form and write a short comment stating that the contents of the information sheet and consent form had been explained to the participant.

3.2 Investigation Protocol

Patients attended the practice for an eye examination without prior knowledge of the study. Each patient was pre-screened by trained practice staff, which included auto-refraction, non-contact tonometry and fundus photography. If a reasonable image was obtained as judged by the pre-screener, the patient was randomly asked if they would be willing to take part in the study. They were given the opportunity to read through the information sheet and sign the consent form whilst they waited for their appointment. In this way, recruitment was not subject to patient selection bias by the investigator, it also reduced pressure on the patient to take part in the study as may have been the case if the patient had been asked in the consulting room. This did however result in some unsuitable patients being recruited, for example: poor images, patients who had undergone refractive surgery which would alter the refraction and IOP, or patients who suffered from glaucoma or ocular hypertension but did not make this known to the pre-screener. These participants were not included in the final analysis. An optometric eye examination was performed, this included: history, refraction, visual acuities and ophthalmoscopy. Blood pressure was measured on the left arm on 3 occasions during the test: after history and symptoms, after refraction and after ophthalmoscopy, the average of the 3 readings was recorded. An Omron M6 upper arm automated blood pressure monitor (Medisave uk) was used, approved by the British Hypertension Society. The patient was given the opportunity to ask questions about the research. The data was recorded in a hand written book during the examination, this included:

1. Participants initials and identification number
2. Age, sex and ethnicity
3. Refraction
4. IOP and BP (average of 3 readings)
5. Relevant systemic and ocular history
6. Medication taken
7. The presence of any family history of glaucoma

Visual fields were carried out on any patient with any suspicion of glaucoma, borderline IOPs or a family member with glaucoma. If suspicion was confirmed, this data was then excluded from the study. It is not normal practice to perform visual field test on every patient. It is accepted that carrying out a visual field examination on every patient would have been preferable, but this was not possible in a busy clinical setting.

Every patient underwent a full optometrist eye examination with an optometrist of 20 years experience; this included a combination of direct and indirect ophthalmoscopy which allowed the discs to be viewed binocularly. Assessment of disc normality was therefore carried out during the examination and only if the optometrist was satisfied that they were normal was the patient included in the study. Disc normality was therefore not limited to the disc photographs.

For the purpose of optic disc analysis, the participant's initials together with their identification number were transferred to a second hand written book, in which the optic nerve measurements were recorded. Both the identification number and initials were used to positively identify the participant and reduce the chance of error. The images were therefore analysed "blind" without knowledge of any of the clinical information. It is however accepted that certain clues from the images are indicative of a participant's age and ethnicity such as drusen and pigmentation. Not all the images were found to be good enough to analyse and some participants had only one good image. All the data was collated onto a spreadsheet for analysis, which would include multiple regression analysis due to large number of different variables recorded.

3.2.1 Participant history

A full history was taken in accordance with the college of optometrists guidelines (Appendix 5). For the purpose of this study, the presence of diabetes, migraine and hypertension were recorded in addition to any medication taken. As no medical records were available, history and medication relied purely on the participant's knowledge. This proved problematic; many participants did not know their medical history or their medication. Other participants reported taking tablets for hypertension but either denied having hypertension or were unaware the tablets were for hypertension. Some participants admitted to not taking their medication regularly, or on the day of the visit. The presence of migraines proved equally difficult to identify, some participants described mild headaches as "migraines" whereas others had more severe classical migraines with visual disturbances and sickness. The differentiation was not clear enough to use in the statistical analysis. These problems are commonly faced by optometrists in practice. For analysis purposes, if the patient responded as having hypertension, diabetes or migraine they were recorded as positive.

3.2.2 Fundus photography

Fig 3.1 Nidek AFC-210 fundus camera



The fundus camera used was a Nidek AFC-210 non mydriatic autofundus camera (birminghamoptical.co.uk). Patients were not dilated for the purposes of this study. The Nidek AFC-210 utilises a Canon EOS 5D DSLR autofocus camera. The camera obtains images from a minimum 4mm pupil, or 3.7mm in the small pupil mode. The images obtained are 45° with 12.8 megapixel imaging. It was important at the start of the study to determine if the fundus camera used was truly Telecentric, (correcting for refractive error in the measurements). This was established by inserting contact lenses of differing powers into one individual to simulate differing refractive errors, powers ranged from -8.00 to +6.00, images were taken and analysed blind with regard to the refractive error. Six separate images were also taken without refractive correction to assess the spread of measurements between different photographs of the same eye (refraction: zero). Spearman's "r" to test for a linear relationship showed no correlations. We can therefore be satisfied that any differences in optic nerve measurements are not due to errors in the analysis with regard to refractive error. It is recognised however, that this does not account for differences in the axial length.

3.2.3 Tonometry

The tonometer used in this study was a Nidek NT-2000 non contact tonometer (birminghamoptical.co.uk). Three readings were taken from each eye and the average was used to reduce IOP variations with the cardiac cycle.

Fig 3.2 Nidek NT-2000 Tonometer



Goldmann tonometry is generally accepted as the gold standard for measuring intraocular pressure and used in a hospital setting almost exclusively. However, in optometric practice, non contact tonometry (NCT) is the most widely used method of measuring intraocular pressure. This is due to the quick, non invasive nature of the test; it can also be done by trained practice staff and is suitable for use in screening. The Nidek NT-2000 uses a stream of air to applanate the cornea and has been shown to have good reproducibility and be comparable to Goldmann (Cho et al 1997).

A pulse of air is used to applanate the cornea. The air pressure is gradually increased, causing the concave corneal shape to flatten. The complete point of flattening is detected optically and the time required used to calculate the air pressure, this in turn is used to calculate the IOP using the Imbert Fick law: This states that the pressure is equal to the force per unit area of applanation for a spherical container.

3.2.4 Blood Pressure Measurements

Blood pressure was measured using an Omron M6 upper arm automated blood pressure monitor, approved by the British Hypertension society. The cuff was positioned on the left arm of each participant and the arm positioned level with the heart with the participant in a seated position.

Fig 3.3 Omron M6 blood pressure monitor



Three measurements were taken: at the beginning of the test, after five minutes and at the end of the test. The average of the three readings was taken, as is recommended by the British hypertension society. The systolic (SBP) and diastolic (DBP) blood pressure were recorded.

3.2.5 Calculation of Ocular Perfusion Pressure

Ocular perfusion pressure is implicated in the pathogenesis of glaucoma. Both raised IOP and low arterial blood pressure act to reduce the ocular perfusion pressure (OPP) to the optic nerve head. OPP is the difference in blood pressure between the ocular arterial and venous vascular beds. If the OPP falls below a critical level, ischaemia can occur. In calculations of OPP, IOP is substituted for venous pressure and systolic blood pressure is substituted for arterial pressure.

The calculation for OPP is given below:

$$\text{OPP} = 2/3 (\text{Diastolic BP} + 1/3 (\text{Systolic BP} - \text{Diastolic BP})) - \text{IOP}$$

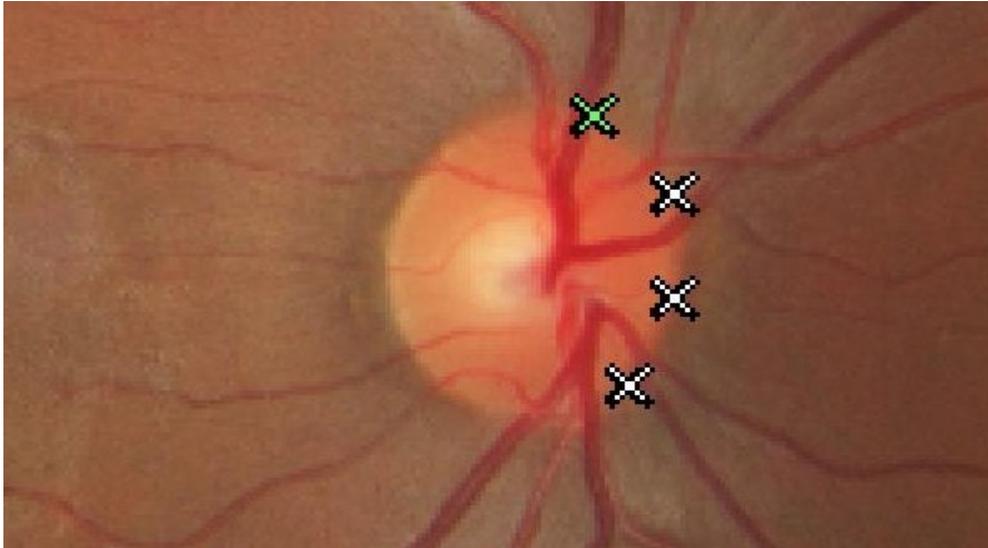
3.3 Image Analysis

3.3.1 Software

The image analysis software used was Navilite by Topcon (birminghamoptical.co.uk). This software allows the observer to trace around the optic disc rim and cup using the mouse pointer, as shown in figure 3.4. The image analysis then links up the points to produce a smooth contour. The software then produces data for the disc and cup

diameters both vertically and horizontally and the disc and cup area, similar data is produced for the cup/disc ratio. Data was recorded in millimetres to three decimal places.

Figure 3.4: Marking the disc rim.



3.3.2 Optic Nerve Head Analysis Protocol

For each optic disc, the disc and cup rims were measured three times to produce three data sets for each parameter; the average was then taken to reduce measurement error. The NRR thickness was measured using manual positioning of a line from the cup edge to the disc edge producing a linear measure of the NRR in the four quadrants, this was also measured three times and the average value used in the analysis. The PPA in each quadrant was measured in the same way. The image analysis is illustrated in figure 2.5:

Figure 3.5: Measurement of the neural retinal rim.



The optic nerve analysis demonstrated some disadvantages:

- The disc edge was not always clearly defined; many discs showed bearing of the sclera canal around the disc edge, clinical judgement was used to define the disc edge.
- Some cups were easy to define, those with deep punched out edges especially (fig 3.6a), however many cups had shallow sloping cups which proved harder to define (fig 3.6b); the colour and displacement of vessels were used to locate the cup edge (fig 3.6c). It is accepted that the use of a stereo viewing system may have increased the accuracy of cup location, however this was not available and because all the images were analysed by one observer, any under or overestimation of cup size should be eliminated. Subjects with poor images were excluded, this was usually due to cataracts (fig 3.6d) or small pupils.
- The optic nerve analysis proved time consuming and produced a large amount of data; this resulted in the photography and analysis of images often being separated by 3 months or longer which ensured the images were analysed without knowledge of the clinical information.

Figure 3.6a: Well defined cup

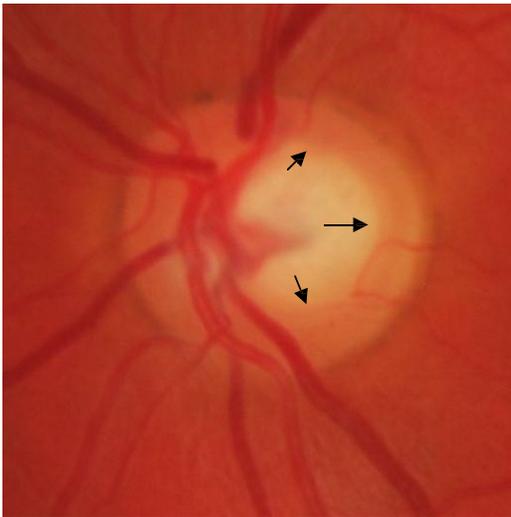
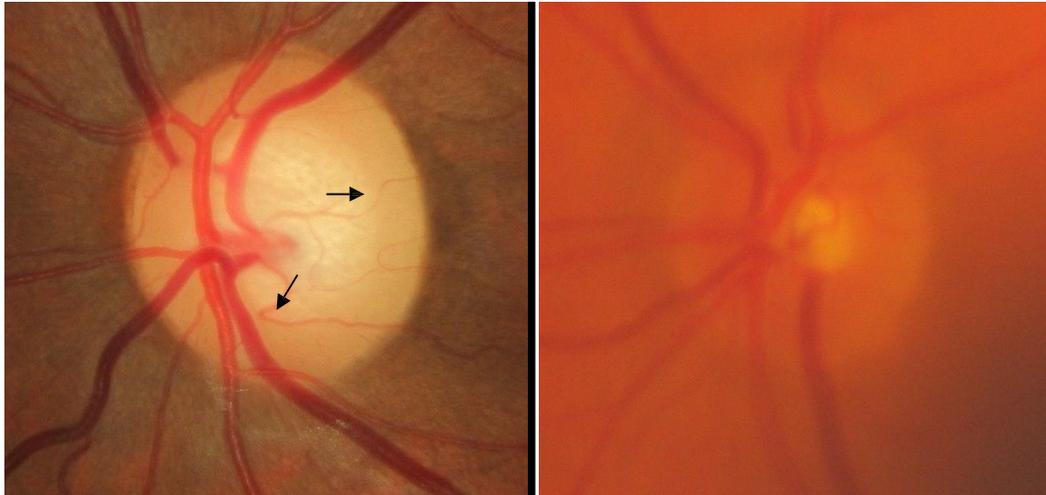


Figure 3.6b: Poorly defined cup



Figure 3.6c: Vessel displacement

Figure 3.6d: Poor image due to cataract



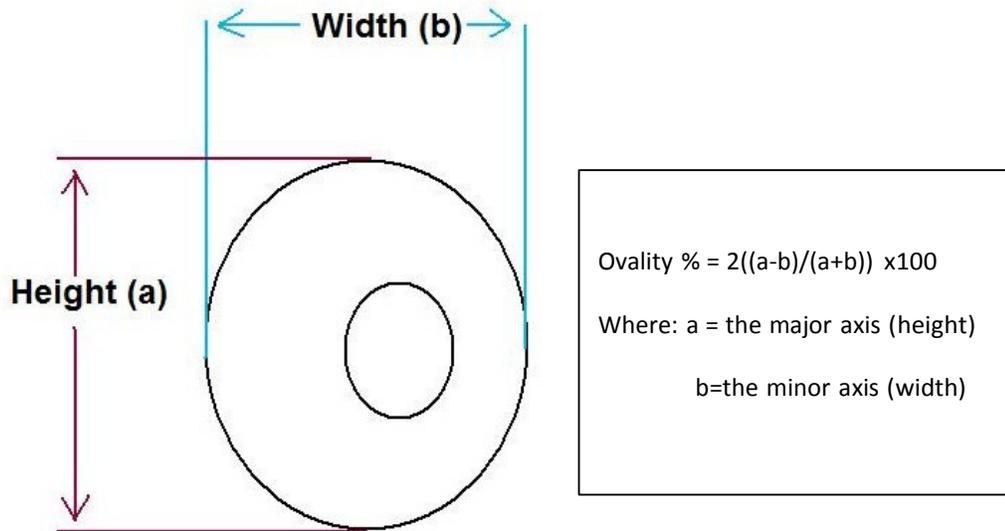
There were however some advantages to this method of image analysis:

- The images were representative of what an optometrist visualises in practice, unlike OCT or NFL imaging, fundus photography image analysis is directly relevant to practice. Although OCT is unquestionably more accurate in disc and cup measurements, due to the need to define a reference plane, the measurement may not exactly relate to the ophthalmoscopic appearance.
- Fundus photography was already used by the practice on all patients as part of their routine eye examination, minimal discomfort or inconvenience was therefore experienced by the patient and the pre-screening staff were already well trained in performing image capture.

Once the images were analysed and the data collected, all the data was collated into a spreadsheet for analysis.

3.3.3 Calculation of Disc and Cup Ovality

It is well known that the normal optic nerve is vertically oval in shape (Jonas 1988). There are few studies in the literature that have looked at the shape or degree of “ovality” of the optic nerve head. It was therefore decided to investigate this and calculate a measure of ovality, both for cup and disc shape. A novel approach was used to measure disc ovality, more frequently used in the area of telecommunications and pipe deformations (Veerappan 2008). The following formula was used:



3.4 Statistical Analysis

This study used several different sample sizes due to stratified sampling such as by ethnic group and age. Investigation of the difference between fellow eyes involved using all eyes with binocular data, the remainder of the study involved using one random eye per subject. Previous studies investigating the normal ONH were used as a guide and have used as few as 56 subjects (Larsson 2011) to many thousands of subjects (Varma 1994). The work by Jonas has been particularly well cited and resulted in the development of the ISNT rule, in his 1988 study, 319 subjects were analysed. Other studies investigating the normal ONH have used: 70 subjects (Jonas 2003), 56 subjects (Larsson 2011), 622 subjects: Bourne (2008) and 459 subjects (Hawker 2005).

Studies into the ethnic ONH differences are based on white vs. African populations and include sample sizes of: 125 subjects (Mansour 1991), Zangwill used 329 white, 24 Hispanic and 74 African subjects (Zangwill 2004) and 70 subjects (Girardin 2007). There are no white vs. Asian studies with which to compare sample sizes. Based on previous studies into ethnic ONH area differences the effect size was calculated at 0.76 (Zangwill 2004). It was postulated that the difference between the SA and WE groups would be less than between the white and African group and so this was lowered to 0.5. Using G*Power tool (<http://www.gpower.hhu.de/en.html>) the estimated sample sizes were $n_1=59$, $n_2=149$ for the two ethnic groups to provide 90% power with an alpha of 0.05 (allocation ratio of 2.5/1).

The ISNT rule has been investigated in other studies and sample sizes have varied from 319 in the original paper by Jonas in 1988 and 177 subjects (Lundmark) to 226 eyes (Iester 2011).

Based on previous studies and the requirement of the data to address both ethnic differences and the ISNT rule, the target sample size was set at 300 WE and 100 SA subjects, assuming a 10% subject rejection rate. The mean and standard deviation was carried out early in the data collection .The statistical analysis was carried out using SPSS v.20.

Chapter 4

Comparison of the optic disc topographic parameters in two ethnic groups: South Asian and White European as determined by fundus photographs in an optometric population

4.1 Abstract

Purpose: This study aimed to evaluate any ethnic differences in optic disc topographic parameters as determined by fundus photography between the South Asian (SA) and White European (WE) population attending an optometric practice.

Methods: This cross sectional study was carried out in North West England between February 2010 and 2011. 269 European White and 91 South Asian participants (mainly Pakistani) were randomly recruited to the study. All patients underwent retinal photography, refraction, intra-ocular pressure and blood pressure measurements. Optic nerve morphology was assessed using a computer aided analysis.

Results: There was no significant difference between the two ethnic groups with regards to: BP, IOP, OPP, refraction or systemic disorders such as migraines or self-reported systemic hypertension. The SA group showed, however, a higher incidence of self-reported diabetes ($p=0.0002$). Both ethnic groups showed a similar degree of IOP asymmetry between fellow eyes. There was no significant difference between the two ethnic groups with regards to optic disc size ($p>0.05$). The SA group however, showed on average statistically greater cupping than the WE group (CDR area: $p=0.032$) and thinner neural retinal rims (nasal NRR: $p=0.0008$), temporal NRR: $p=0.0039$, Inferior NRR: $p=0.045$). The SA optic discs were more vertically oval than the WE group ($p=0.004$). The degree of PPA was not statistically different between groups, PPA in the temporal sector was found in 50% eyes, nasal PPA was found in 19.8% of WE eyes and 8.7% of SA eyes. No statistically significant differences in inter-eye differences were found between the two ethnic groups.

Conclusion: In the absence of glaucoma, South Asian subjects have greater cupping, thinner neural retinal rims and more vertically oval discs than the European White population, with no difference in optic nerve size or inter-eye asymmetry between the two groups. This is an important consideration when screening the UK population for glaucoma.

4.2 Introduction

In the UK, the largest ethnic minority is South Asian (SA), principally of Indian and Pakistani origin. There is a lack of knowledge regarding ethnic differences between SA and the White European (WE) populations. Currently to our knowledge, no study has investigated these two populations in parallel. It has previously been suggested that SAs have a larger disc size (Nangia et al 2008, Mansour et al 1991). However, any comparisons between cupping and NRR area have not yet been addressed. Given the large SA population in the U.K, knowledge of any racial differences in the optic disc topography as assessed in optometric practice is important for glaucoma screening. A recent American study looked at the prevalence of open angle glaucoma (OAG) in multiple ethnic groups (Stein et al 2011) and concluded a higher prevalence of OAG in the Pakistani group compared to Whites. The Pakistani sample size however was small. It would be reasonable to extrapolate these findings to the UK. The ethnic diversity of the UK population is shown in table 3.1

Studies in Asia have been conducted on the Indian and Pakistani populations; Conclusions regarding ethnic differences between these groups and the White population have all been drawn from different studies either by the same author (Jonas 2003) or from studies by different authors using different methodologies (Nangia 2008). It is therefore difficult to directly compare the results; as an example, in two Indian studies: Sekhar et al (2001) used a fundus camera and found the average disc size to be 3.37mm^2 compared with the study by Nagia and Jonas (2008) which found the average to be 2.25mm^2 by OCT. Therefore, it may be more relevant to compare C/D ratios and NRR ratios than absolute values when comparing ethnic differences between studies.

This is the first study to the author's knowledge to directly compare the South Asian UK population with the UK White population in the same study.

4.3 Study aims

The aim of this study is to compare the normal optic nerve head appearance between the two ethnic groups: White European and South Asian.

4.4 Subjects and Methods

4.4.1 Recruitment of participants

Participants free from optic nerve disease were recruited to this study as they attended for an optometric eye examination in a high street practice. Exclusions are given in section 2.1.1.

4.4.2 Ethics approval

Ethical approval was obtained from the Aston University ethical approval committee prior to the start of this study. The study was designed and conducted according to the principles of the Declaration of Helsinki.

4.4.3 Methods

Details of the investigations and methods are given in Chapter 2. The participants were asked to tick their ethnic background on the consent form. The vast majority of patients gave their ethnic group as White or Pakistani, a small number were Indian or Bangladeshi. Less than 5 patients fell into other categories, these patients were excluded from this study. When the patient was unable to read or understand English, a translator was used to explain the study and translate the information sheet and consent form, this was usually a family member. The translator was also asked to sign the consent form. Each patient was questioned regarding their general health; the results represent the patient's responses, as access to their medical records was not available. The actual blood pressure of each patient on the day of the visit was recorded, some patients with normal blood pressure were on treatment for hypertension, however the severity and duration was unknown.

4.4.4 Statistical Analysis

The systemic parameters were tested for normality in each ethnic group using the Shapiro-Wilk test for normality (table 4.1) and the two groups compared using Pearson's simple correlations and unpaired t-tests. The chi-squared test was used to compare the non-normally distributed data and age grouped data. Differences in ONH parameters between the two groups were investigated using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) statistics.

4.5 Results

4.5.1 Patient Demographics

269 WE and 91 SA subjects were included in this study. Of the South Asian group, 86 were Pakistani, 3 were Bangladeshi and 2 were Indian. All the parameters measured were different in both ethnic groups with the exception of IOP which showed no significant difference ($p=0.526$). The differences between groups are shown in table 4.2 together with the general characteristics.

Table 4.1: Systemic data test for normality

Shapiro-Wilk test for normality p - values		
Parameter	SA[†] (n=91)	WE[†] (n=269)
IOP	0.311	0.246
BP systolic	0.17	0.099
BP diastolic	0.148	0.023*
OPP	0.152	0.107
Age	0.24	0.001**
RX	0.00**	0.001**

* Normally distributed on visual inspection of histogram and Q-Q plot in SPSS
 ** not normally distributed
 † SA=South Asian WE=White European

Table 4.2: General characteristics SA and WE: (Students unpaired t-test).

Parameter	SA[†] n=91 Median, Range	WE[†] n=269 Median, Range	p-value
Age	38, 21	53, 21	<0.0001*
Refraction (BVS)	-0.25, 2	0.25, 2	<0.0001*
	Mean ± SD	Mean ± SD	p-value
IOP	14.89 ± 2.597	15.09 ± 2.781	0.526
BP systolic	119.30 ± 16.419	129.35 ± 17.864	<0.0001*
BP diastolic	71.23 ± 9.754	75.34 ± 10.588	0.001*
OPP	43.28 ± 7.284	47.21 ± 8.167	<0.0001*
Gender	males:43 females:48	males:107 females 162	0.085

*significant at p<0.05 † SA=South Asian WE=White European

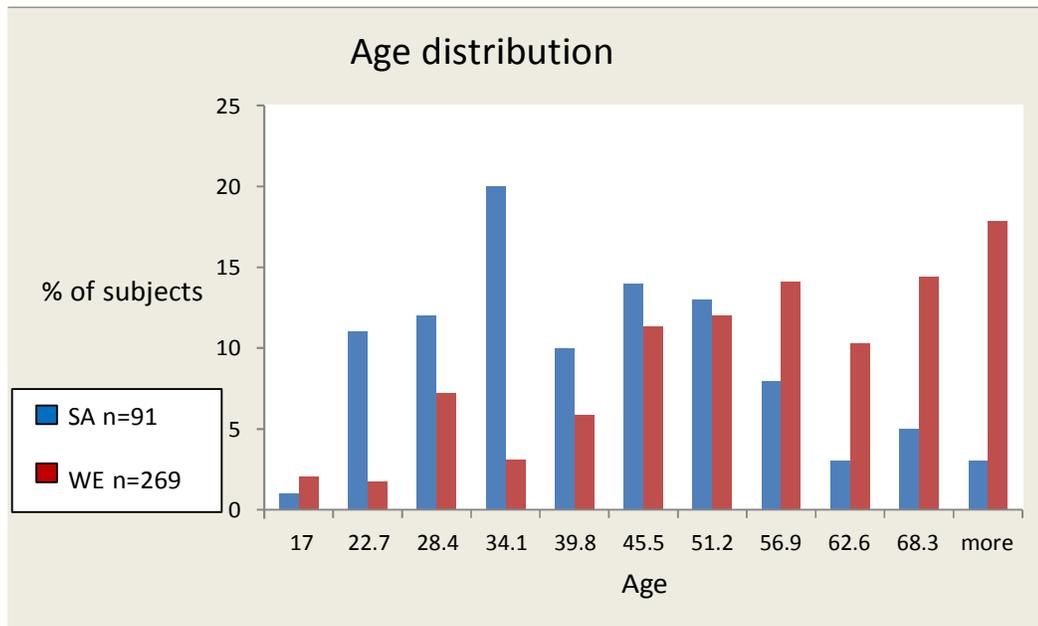
4.5.2 Gender

The gender differences between each ethnic group were not statistically different: chi-squared test: 1.564, p=0.085. The effect of gender on the ONH was analysed for each ethnic group using forward stepwise multiple regression. Only the WE group (n=257) showed gender to have a statistically significant effect on the ONH parameters. Males showed larger horizontal cup diameters ($\beta = -0.216$, p=0.008) and larger vertical CDRs ($\beta = -0.231$, p=0.003). Females showed greater disc ovality ($\beta = 0.213$, p=0.008) and thicker inferior NRRs ($\beta = 0.209$, p=0.017). No effect of gender was found in the SA group (n=91). Further analysis for gender can be found in appendix 7.

4.5.3 Age

The SA group comprised of a younger age sample than the white group. This is illustrated in figure 4.1 which shows the skew to older age in the WE group, this difference was statistically significant ($p < 0.001$), requiring analysis of any ethnic differences to be corrected for age.

Figure 4.1 Study population: Age demographics (South Asian vs. White European)



4.5.4 IOP

There were no statistical differences between the two ethnic groups in either a t-test or when the data was corrected for age: ANCOVA $p > 0.05$. There was no significant correlation between IOP with patient age in either ethnic group (Pearson's $p > 0.05$).

4.5.5 BP and OPP

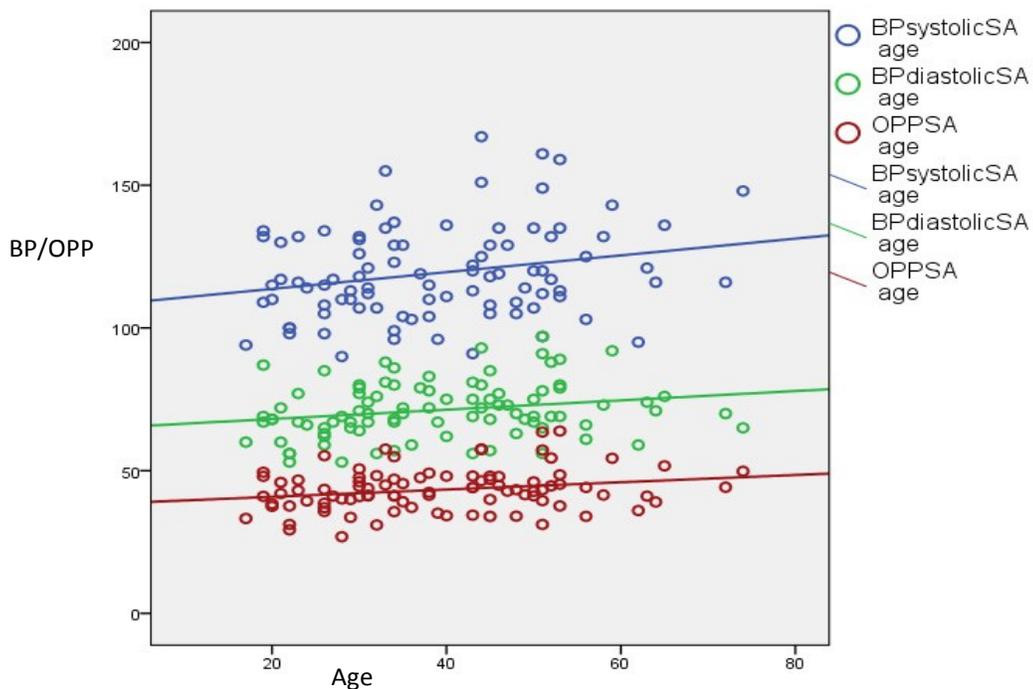
Table 4.2 shows higher OPP and BP in the WE group. The differences were re-examined in an ANCOVA corrected for age to show any real differences between the groups, the results are shown in table 4.3. After correcting for age, the systolic and diastolic BP remained statistically significantly different ($p = 0.041$ and $p = 0.038$); the OPP however was no longer significantly different between the two groups

Table 4.3: Systemic parameters: ANCOVA corrected for age

parameter	ANCOVA corrected for age p-value	Estimated means corrected for age	
		WE (n=269)	SA (n=91)
BP systolic	0.041	127.854	123.552
BP diastolic	0.038	74.989	72.208
OPP	0.053	46.687	44.77
RX	0.063	0.105	-0.389

The correlation of both systolic and diastolic blood pressure with age was assessed in both ethnic groups and is shown in figures 4.2 and 4.3

Figure 4.2: SA population(n=91): correlation of age vs BP/OPP



Correlation shows how two age and BP are related to each other, although one can be used to predict the other, it does not tell us how they are related; as they may correlate with another common variable or variables such as weight or exercise.

Pearson's correlation found an increase in systemic blood pressure and OPP with age in both ethnic groups, this was statistically significant ($p < 0.05$) and was more pronounced in the WE group, reflecting the higher numbers of older subjects in this group. It was therefore necessary to correct for age when considering any differences between the two ethnic groups.

Figure 4.3: WE population(n=269): Correlation of age vs BP/OPP

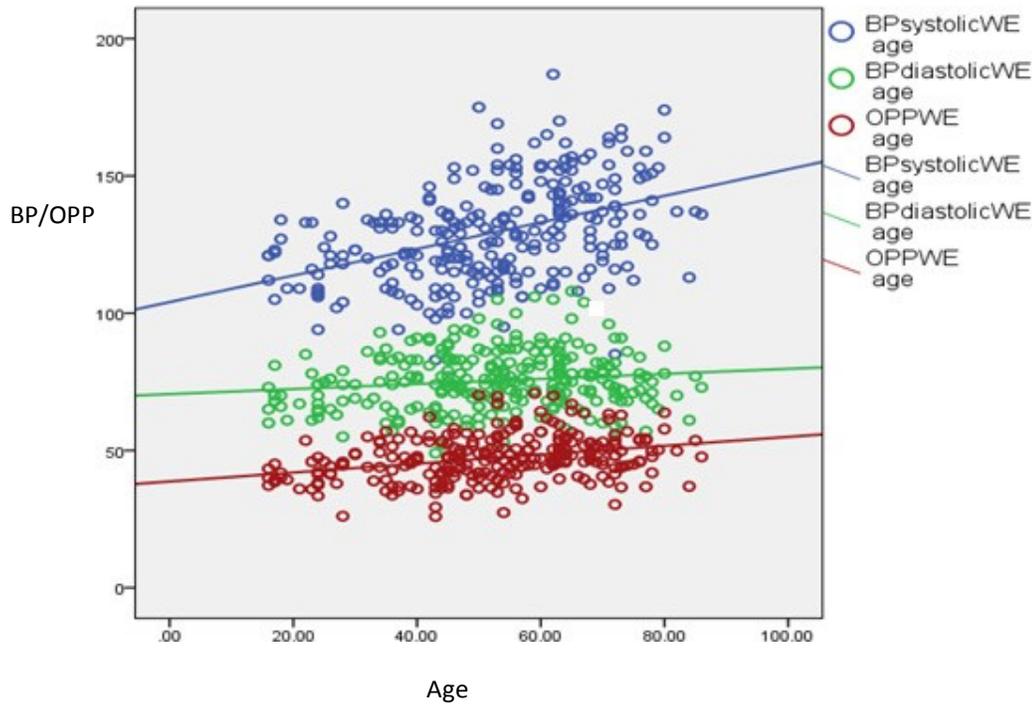


Table 4.4 Correlation coefficients (Pearson's): blood pressure versus age

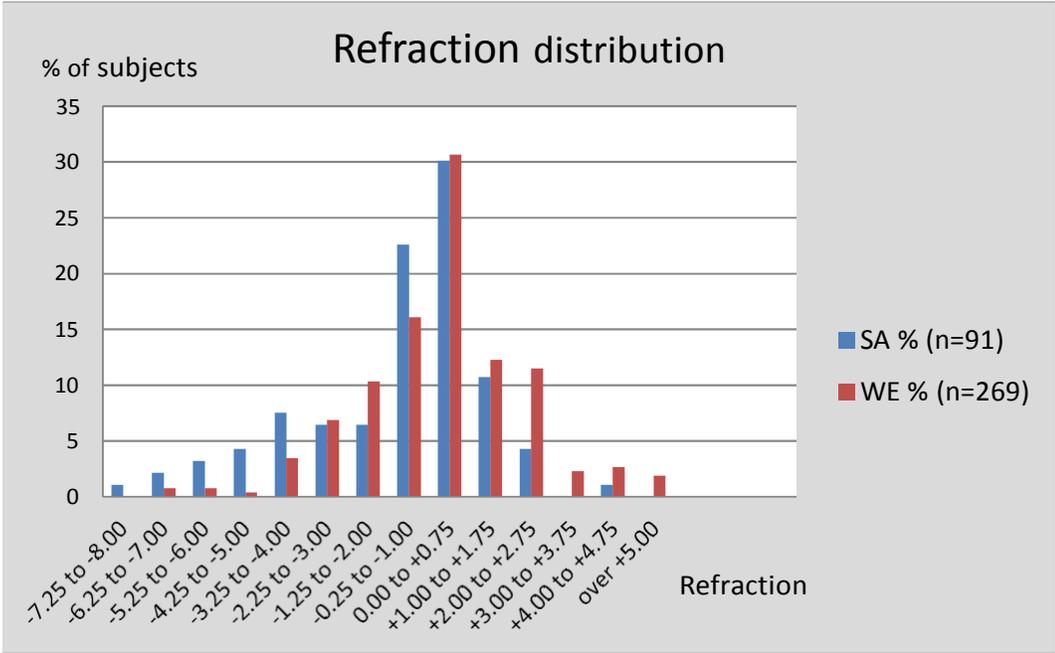
Ethnicity	BP systolic	BP diastolic	OPP
South Asian	0.237 (p=0.023)*	0.222 (p=0.033)*	0.232 (p=0.26)*
White European	0.431 (p<0.0001)*	0.139 (p=0.023)*	0.317 (p<0.0001)*

* Significant at p<0.05

4.5.6 Refraction

The refraction for each eye was recorded as the best vision sphere. The WE population showed a skew to hyperopia (figure 4.4), however it is well known that there is a shift to hyperopia with increasing age. Once the refraction data was corrected for age, there was no significant difference in refraction between the two groups (p>0.05).

Figure 4.4: Refraction distribution (South Asian vs. White European)



4.5.7 History of vascular disease

The self reported results for each ethnic group in shown in table 4.5 together with the p-values. The SA group showed a higher incidence of hypertension, diabetes, migraine and headaches. However, only diabetes was statistically significant between the two ethnic groups (p=0.0002).

Table 4.5: Vascular Disease Self-reported (Chi-squared test):

	WE† n=269	SA† n=91	Chi squared	p value
Headaches	5	3	0.647	0.421
Migraines	8	5	1.241	0.265
Hypertension	71	16	2.881	0.090
Diabetes	12	15	14.167	0.0002*
Both Diabetes and Hypertension	9	9	6.131	0.013*

*significant at p<0.05.

† SA=South Asian, WE = European White

Diabetes was not only more prevalent in the SA group, but tended to occur at an earlier age than the WE group, see table 4.6.

Table 4.6: Vascular disease by age group

	WE [†] n = 269			SA [†] n = 91		
	<40 n=60	41-60 n=116	>60 n=93	<40 n=51	41-60 n=34	>60 n=6
Age group						
Headaches	3	2	0	2	1	0
Migraines	3	2	2	2	1	0
Hypertension	0	26	45	2	12	2
Diabetes	1	6	8	2	10	3
Both Diabetes and Hypertension	0	3	6	1	7	1

[†]SA = South Asian, WE = White European

For both ethnic groups combined, the ONH appearance was not statistically correlated with age, gender, refraction, IOP or vascular status. Further information can be found in appendix 7

4.5.8 Inter-ocular differences

Disc asymmetry was investigated in both ethnic groups and compared. For this part of the analysis, only subjects with two clear images could be included. In addition, subjects with anisometropia over 2.00D were also excluded to rule out the possible influence of refraction. The ethnic groups comprised: 91 SA and 252 WE participants. The inter-eye differences were analysed with respect to ethnic group. The WE group showed a greater inter-eye differences in horizontal disc diameter ($p=0.005$), vertical disc diameter ($p=0.017$), disc area ($p=0.025$) and NRR area ($p=0.028$) compared with the SA group. The SA group showed a greater inter-ocular difference in vertical cup diameter ($p=0.024$): however after Holms sequentially rejective method was used for significance correction of multiple comparisons, no statistically significant differences remained between the SA and WE groups with regard to asymmetry ($p>0.05$). IOP and the remaining ONH parameters showed no significant inter-eye difference between the two ethnic groups. The results are shown in table 4.7.

Table 4.7: Ethnic Inter-eye differences (ANCOVA corrected for age)

Parameter	SA [†] inter-eye diff Mean ± SD	WE [†] inter-eye diff Mean ± SD	ANCOVA p	p2 (p-value after Bonferroni)
IOP	1.080 ± 1.061	1.005 ± 0.758	0.447	NS
V disc diameter	0.069 ± 0.055	0.093 ± 0.090	0.017	NS
H disc diameter	0.069 ± 0.053	0.101 ± 0.103	0.005	NS
Disc area	0.159 ± 0.123	0.216 ± 0.230	0.025	NS
V cup diameter	0.137 ± 0.142	0.118 ± 0.124	0.024	NS
H cup diameter	0.129 ± 0.137	0.119 ± 0.130	0.536	NS
Cup area	0.106 ± 0.093	0.097 ± 0.109	0.502	NS
Vertical CDR	0.065 ± 0.070	0.069 ± 0.096	0.738	NS
Horizontal CDR	0.069 ± 0.067	0.062 ± 0.065	0.398	NS
CDR area	0.040 ± 0.032	0.036 ± 0.039	0.429	NS
NRR area	0.140 ± 0.128	0.193 ± 0.216	0.028	NS
Inferior NRR	0.078 ± 0.080	0.074 ± 0.083	0.736	NS
Superior NRR	0.077 ± 0.080	0.071 ± 0.084	0.058	NS
Nasal NRR	0.068 ± 0.057	0.085 ± 0.071	0.037	NS
Temporal NRR	0.080 ± 0.089	0.076 ± 0.085	0.067	NS

* p-value after Holms-Bonferroni correction † SA = South Asian, WE = White European

More in depth results of the inter-eye differences including combined ethnic group results can be found in appendix 6.

4.5.9 Ethnic differences in optic disc parameters

In order to compare the optic disc parameters between the two ethnic groups, the data was corrected for age in an ANCOVA model for each ONH parameter and significance corrected using the Holms-Bonferroni sequential rejection method for multiple comparisons, the results are shown in table 4.8.

The age corrected data showed no significant difference in either horizontal or vertical optic disc size between the two groups ($p>0.01$). The SA discs were however, more vertically oval in shape compared with the WE group, this was statistically significant ($p=0.0002$). The ovality of the cup was not statistically different between the two groups, however this measure showed a large standard deviation. The SA group demonstrated a larger CDR area compared with the WE group ($p=0.0044$). The SA group also showed more vertical cupping compared with the WE group showing that the increased cupping was due to a vertical enlargement of the cup. The WE group showed a much higher proportion of flat discs ($CDR \leq 0.1$) compared to the SA group.

Table 4.8: Optic Nerve Head comparisons: between ethnic groups: ANCOVA corrected for age (SA n=91 WE n=269)

Parameter	SA [†] mean \pm SD	WE [†] mean \pm SD	p-value	p2*-value
Disc Diameter V	1.828 \pm 0.156	1.794 \pm 0.178	0.230	NS
Disc Diameter H	1.632 \pm 0.145	1.678 \pm 0.189	0.384	NS
Disc Area	2.309 \pm 0.347	2.368 \pm 0.449	0.884	NS
Disc Ovality %*	11.321 \pm 8.665	6.823 \pm 7.870	0.00024	0.0044*
Cup Diameter V*	0.756 \pm 0.271	0.618 \pm 0.318	0.00030	0.0052*
Cup Diameter H	0.676 \pm 0.269	0.574 \pm 0.302	0.007	NS
Cup ovality %	8.181 \pm 29.025	7.129 \pm 16.763	0.281	NS
Cup Area	0.447 \pm 0.249	0.356 \pm 0.261	0.004	NS
CDR V	0.410 \pm 0.134	0.357 \pm 0.168	0.008	NS
CDR H*	0.416 \pm 0.139	0.343 \pm 0.156	0.00036	0.0058*
CDR Area*	0.191 \pm 0.084	0.158 \pm 0.088	0.002	0.032*
NRR Area	1.861 \pm 0.283	2.018 \pm 0.398	0.022	NS
NRR Inferior*	0.545 \pm 0.127	0.597 \pm 0.149	0.003	0.045*
NRR Superior	0.482 \pm 0.141	0.548 \pm 0.171	0.004	NS
NRR Nasal*	0.553 \pm 0.109	0.636 \pm 0.144	0.00004	0.0008*
NRR Temporal*	0.354 \pm 0.126	0.442 \pm 0.180	0.0002	0.0038*
PPA Inferior	0.035 \pm 0.095	0.037 \pm 0.102	0.62	NS
PPA Superior	0.002 \pm 0.018	0.014 \pm 0.062	0.15	NS
PPA Nasal	0.017 \pm 0.057	0.039 \pm 0.100	0.126	NS
PPA Temporal	0.108 \pm 0.129	0.118 \pm 0.147	0.867	NS

* Significant at $p<0.05$ after Holms-Bonferroni correction

[†] SA = South Asian, WE = White European

The amount of PPA around the discs showed no significant difference between the two groups in any quadrant. Peripapillary atrophy was found in 19.8% of the WE participants

and 8.7% of the SA participants (age matched data). Far more subjects showed temporal PPA: 49.5% of WE subjects and 46.7% of SA subjects. Therefore, both Ethnic groups show PPA in the temporal sector with an incidence of approximately 50%

The thickness of the neural retinal rim in each quadrant was compared between the two age matched groups. The WE group were found to have statistically thicker neural retinal rims in the inferior, nasal and temporal rims compared with the SA group ($p=0.045$, $p=0.0008$ and $p=0.0038$ respectively). The NRR thickness distribution and abeyance to the ISNT rule is further explored in chapter 5.

4.6 Discussion

4.6.1 Main findings

There was no significant difference in the optic disc size between the SA and WE groups. The SA group, however, had discs that showed a larger degree of cupping and thinner neural retinal rims than the WE group. The SA group, were also observed to have greater vertical disc ovality than the WE group, but the cup ovality was not significantly different. There was no statistical difference between the WE and SA ethnic groups with regards to IOP and OPP when corrected for age ($p>0.05$).

4.6.2 Ethnic differences: Optic nerve head and cupping

This study found no statistical difference in the disc size between the SA and WE groups; this is in agreement with a study published by Jonas et al (2003). Other papers have suggested that the Indian population have larger discs (Nangia et al 2008, Mansour et al 1991), however these authors use data from different studies. However a study in 2011 by Arvind et al, investigated the normal ONH in the south Indian population, and found larger disc areas (2.82 ± 0.52) but similar cup area (0.53 ± 0.39) to the present study, the vertical CDR was also similar: 0.36 ± 0.18 compared with the present study (Arvind et al 2011).

The disc shape was more vertically oval in the SA group, particularly in females; the disc shape has not previously been investigated in the Asian population but increased ovality has been found in African subjects (Quigley 1990). The ovality measure is relevant to glaucoma screening, as vertical enlargement of the cup is a recognised sign of early glaucoma. It has been reported that if a disc is vertically oval, it is more likely to have an oval cup (Tomlinson 1974). However the data from the present study shows that the SA population exhibit more vertically oval discs without increased cup ovality, a vertical enlargement of a SA cup in the vertically oval disc could therefore be overlooked as normal.

The degree of cupping in the SA discs was greater than in WE discs. This has not been previously reported, due to an absence of any studies investigating these two groups. Comparisons have been drawn using disc size data from different studies, however it is harder to compare cupping due to differences of measurement. There has also been a move away from measuring cupping and the CDR towards NRR and ONH size measurement due to the use of HRT. Another interesting difference between the two groups was the very small percentage of SA discs that were either flat or had a CDR of ≤ 0.2 compared with the WE population.

4.6.3 Ethnic differences: Neural retinal rim thickness

The neural retinal rim was thinner in the SA group in the inferior, nasal and temporal quadrants, but showed a similar distribution in both ethnic groups. In both groups, the thickest rim was nasal followed by inferior and superior and was thinnest in the temporal rim. An Indian based study by Jonas et al in 2003, found the temporal rim to be the thinnest but that the other three quadrants did not vary markedly in their rim thickness (Jonas 2003); this is in agreement with the present study. The thinner NRR in the SA group may suggest some differences in the anatomy of the ONH with regard to less glial tissue or connective tissue support to the nerve fibres. This may support the notion that the SA population are more susceptible to normal tension glaucoma than the White population.

Combining the ethnic groups, despite no difference in ONH size with gender, males tended to have more vertically oval discs with thicker inferior NRRs than males, this was highly significant and is likely to reflect real genetic differences between the genders (appendix 7). WE males also demonstrated increased horizontal cupping and larger vertical CDRs by virtue of their less vertically oval shape. These gender differences were not found in the SA group, perhaps due to the increased vertical ovality of SA discs in both genders. Few studies have addressed gender differences in ONH shape, both Quigley et al (1990) and Mansour et al (1991) found females to have a shorter horizontal disc diameter which is agreement with the present study. The most statistically significant finding with gender was the increased vertically oval disc shape found in WE females.

4.6.4 Ethnic differences: Inter-eye differences

The right and left eyes within individuals were highly correlated for all ocular parameters and IOP. The IOP varied on average by less than 1mmHg, the upper limit of asymmetry was 3mmHg (mean+2SD) and the cup area by 0.1mm^2 , the upper limit of cup area asymmetry was 0.3mm (mean=2SD). Both groups showed a similar degree of IOP asymmetry between fellow eyes. The only ocular parameter to show significance between

the two ethnic groups was the horizontal disc diameter ($p=0.005$), However after Holms-Bonferroni correction, this was no longer significant at $p<0.05$. The WE group also showed a greater standard deviation for intraocular differences than the SA group for disc area and NRR area, showing a greater spread of disc sizes for this group. These results show that although the differences are small, the WE group do exhibit larger amounts of inter-ocular variation for some variables than the SA group. It is also worth note that the CDR does not show any difference in inter-ocular variation between fellow eyes between the two ethnic groups. This has not previously been reported and is useful in glaucoma screening when the CDR rule of 0.2 can equally be applied to both ethnic groups.

4.6.5 Reporting of Glaucoma Family History

This study found that the SA group were far less likely to report a family history of glaucoma, even when the groups were age matched. Possible reasons for this include: undiagnosed disease, family members living abroad, a lack of knowledge of the genetic nature of glaucoma and unwillingness to discuss illness with family. It is also possible that glaucoma does not show the same genetic expression in all ethnic groups, it is possible that more cases could occur spontaneously. This area warrants further study.

The WE population comprised of an older age sample than the SA group, this is consistent with the optometric population; fewer elderly SA patients tend to attend for an eye examination than white patients. This may be due to a lack of knowledge regarding eye disease and the importance of eye examinations, reduced visual expectations with age or language difficulties which deter them from attending, it is therefore likely that undiagnosed glaucoma cases is greater in the SA population.

4.6.6 Clinical Relevance

The anatomical difference between the two ethnic groups is important for glaucoma screening in the UK. The knowledge that the NRR is thinner in the Asian population, but that the thickness distribution follows that of the white population will assist the clinician when screening the population for glaucoma. It is also important to note that flat discs are more unusual and a greater degree of cupping more common in the Asian group, this could potentially result in more false positive referrals into the hospital eye service. The SA discs were also more likely to be vertically oval; importantly it could also mean that a vertical enlargement of the cup in a vertically oval disc may be overlooked. It is also of clinical relevance to know that inter-eye asymmetry is similar in both ethnic groups and that a CDR of <0.2 can be used as the cut off for disc asymmetry.

Studies using HRT and OCT rather than fundus images will give different results, HRT gives a smaller ONH area (Thomas et al 2005) but larger rim area (Jonas 1998) than

photographs. OCT and HRT measurements have also been shown not to be interchangeable (Seymenoğlu et al 2013), with OCT giving on average larger measurements than the HRT. A race specific programme for the HRT has been developed for Black and White subjects which improved sensitivity for both groups but decreased specificity for the Black group (Zelevsky 2006). The HRT III contains 104 Asian Indians in its database but this has not been found to improve the diagnostic ability (Knight 2012). The current study suggests a larger HRT profile may be useful for the Asian group to account for the ethnic differences in the UK and may increase specificity in this group. Glaucoma screening at a clinical level in practice should consider the gender differences regarding ONH shape and cupping. Females of WE origin have more vertically oval discs compared with WE males, but without a corresponding increase in cup ovality, this needs to be considered when assessing a disc for the ISNT rule. Theoretically, such a disc could lose some NRR at the 12 and 6 o'clock position and still obey the ISNT rule.

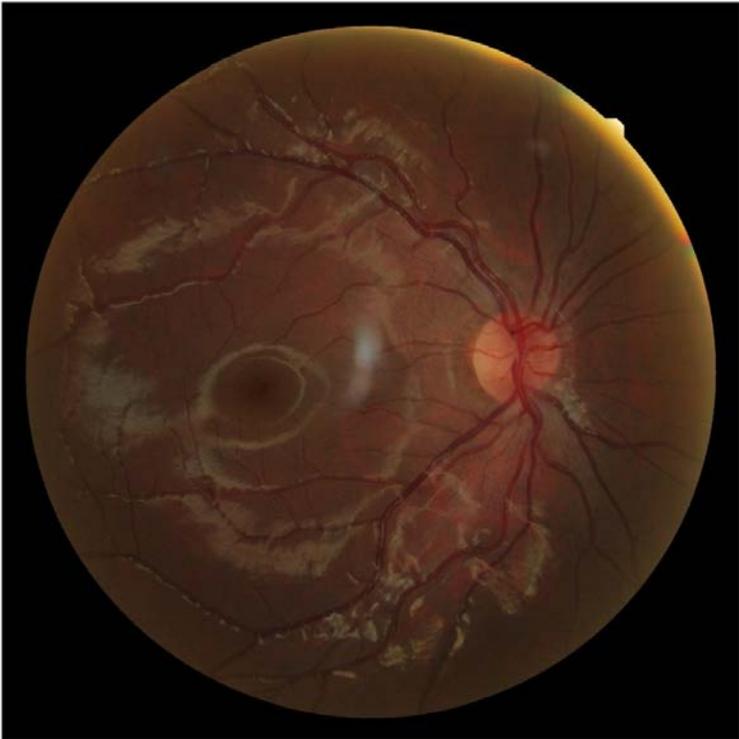
Best practice is Goldmann tonometry on two occasions, visual field assessment and ophthalmoscopic evaluation prior to referral. Knowledge of the ethnic differences will assist in borderline cases, the low reporting of a family history despite the higher incidence of glaucoma in the Asian group must also be considered.

4.6.7 Study Limitations

The ONH analysis was carried out blind with regard to the demographics of the patient, it is however acknowledged that certain clues were often present regarding the patient's age and ethnicity. The SA population tended to have a darker fundus appearance than the WE population, and younger patients tended to have highly reflective retinal images, a factor that can prove problematic in computerised image analysis (see figure 4.5). Older patients often had macula changes and drusen. However all the images were measured prior to any analysis.

Only a small number of patients reported a family history of glaucoma or demonstrated PPA in the nasal quadrant, which made analysis and the drawing of conclusions problematic. It was also limited by the lack of access to the patient's medical history with regards to their vascular health, the patient's response was recorded which may not always have been accurate, the figures given here must therefore be regarded as estimates rather than absolute values. It does however; highlight the difficulties of obtaining an accurate history from the patient during an optometric assessment. There was also room for error in assessing the cup size. Due to the variation both in cup size and cup depth, it cannot be assumed that measurements errors were in the same direction.

Figure 4.5: Highly reflective image in a young SA patient



Chapter 5

An investigation of the “ISNT rule in normal eyes as determined by fundus photographs in an optometric population

5.1 Abstract

Purpose: This study aimed to evaluate the validity of the “ISNT” rule in normal eyes, and to determine the proportion of the general population that adheres to this rule. Factors affecting the NRR thickness in the four sectors will also be investigated with regards to ocular and systemic variables.

Methods: This cross sectional study was carried out in North West England between February 2010 and February 2011. 298 patients were randomly recruited to the study. All patients underwent retinal photography, refraction, intra-ocular pressure and blood pressure measurements. Optic nerve morphology was assessed using computer aided analysis; the NRR thickness was measured by observer location of the NRR edges and compared between the four sectors for adherence to the ISNT rule.

Results: 5.7% of normal eyes obeyed the ISNT rule, with 75.9% showing thicker inferior than superior rims, 14.4% showing thicker superior than nasal rims and 98% showing thicker nasal than temporal rims. Removing the nasal sector from the analysis resulted in 74.6% of normal eyes following a NRR thickness pattern of: inferior>superior>temporal (IST rule). Vertically oval discs tend to have thinner nasal NRRs and are more likely to obey the ISNT rule. With increasing age, the inferior: superior NRR ratio decreases, with older eyes less likely to obey both the ISNT and IST rule.

Conclusion: The ISNT rule has a low adherence by normal eyes and would be better replaced by the IST rule, disregarding the nasal sector which is the last to be affected by glaucoma and shows a high degree of variability due to variable insertion of the retinal trunk vessels. In addition, more vertically oval discs which are more likely to obey the ISNT rule, are no more likely to obey the IST rule. The IST rule is therefore more suitable for assessing discs of all shapes. The use of the IST rule in glaucoma detection requires further study in adherence to the rule by eyes with early glaucoma, only if there is a difference between these two groups should the rule be adopted in glaucoma screening. This study suggests that in current clinical practice, the IST rule rather than the ISNT rule should be assessed for normality, and the use of the rule should not be used as a definitive screening test for glaucoma. Care should also be taken when assessing vertically oval discs, placing greater emphasis on the inferior>superior>temporal ratios

5.2 Introduction

Glaucoma screening in optometry is generally carried out in patients aged over 40 years of age and involves a triad of disc assessment, IOP and visual field examination, although for those with a family history or deemed to be at risk, these may be carried out at a younger age. Assessment of the disc is usually carried out using direct or indirect ophthalmoscopy. Increasingly, fundus photography is also used in optometry. Imaging instruments such as the HRT and OCT are not widely available in a primary care setting. It is therefore crucial that the optic disc is carefully assessed by the clinician. The original concept of the cup/disc ratio proposed by Armaly (Armaly 1967) is widely used in optometry and is useful for monitoring change; however this has been superseded by photography. The usefulness of the cup/disc ratio is limited in glaucoma screening unless the disc size is taken into account, something that is rarely done by optometrists. The ISNT rule is a way of assessing optic disc normality, independent of disc size by looking at the relative NRR thickness in each quadrant.

The ISNT rule is based on the clinical findings of Jonas (Jonas et al 1988) who examined 457 normal eyes and found that the neuro-retinal rim thickness followed the pattern of inferior, superior, nasal and temporal in decreasing thickness order. This has been adopted into clinical practice as a quick and easy way of assessing the optic nerve for normality. However, subsequent studies by the same author (Jonas 1989, 2003) found that although the temporal rim was the thinnest, the inferior, superior and nasal NRR were similar in thickness. This is surprising, considering how the ISNT rule has been adopted as a rule of thumb in the absence of any evidence based studies to validate its use in glaucoma screening. Several studies have since questioned its usefulness both in assessing normality (Sihota et al 2008, Pogrebniak et al 2009, Lester 2011) and in screening for glaucoma (Morgan et al 2012).

5.3 Study aims

This section of the study aims to investigate the commonly used ISNT rule in assessing the ONH for glaucoma. The numbers of discs that obey the ISNT rule were investigated together with the overall mean distribution of NRR thickness. Adherence to the ISNT rule was also compared in different cup sizes: small, medium and large. Multiple regression with ocular and non ocular factors was also investigated, which included the influence of disc size and shape, age, ethnicity and gender.

5.4 Subjects and Methods

5.4.1 Recruitment of participants

Three hundred and sixty participants were examined in the present study as they attended for an optometric eye examination in a high street practice. Due to exclusion of eyes with a CDR of 0.2 or less (62 eyes), 298 patients free from optic nerve disease were included in the final analyses. This exclusion was based on the fact that discs with a CDR of 0.2 have less definable cups that do not allow an accurate measurement of the NRR thickness in the 4 meridians and the image analysis software was unable to measure CDRs below 0.2. Other exclusions are given in section 3.1.1

5.4.2 Ethics approval

Ethical approval was obtained from the Aston University ethics committee prior to the start of this study. The study was designed and conducted according to the principles of the Declaration of Helsinki.

5.4.3 Methods

Details of the investigations and methods are given in Chapter 2. Optic disc analysis was carried out using retinal photography and Navis-lite software. The NRR thickness for each ONH was measured in 4 sectors: inferior, superior, nasal and temporal. This was achieved by marking the cup and disc outline and drawing a line between the disc and cup margin using the mouse pointer. The average value of 3 measurements was recorded. This interpretation of the ISNT rule is intended to mirror the assessment used in optometric practice by visual assessment rather than more complex methods using sectors and area measurements which are difficult to apply in practice.

5.4.4 Statistical Analysis

One eye from each subject was randomly selected to be included in the study, done by alternately selecting right eye/left eye throughout the data set. The NRR thickness was compared manually in each of the 4 sectors, an eye was considered to obey the ISNT rule if the pattern of NRR thickness followed the I>S>N>T pattern. Eyes were assessed for adherence to the ISNT rule and any influence of cup size, disc size, and shape. The discs were further subdivided into small cups (CDR 0.2-0.4), medium cups (CDR 0.45-0.6) and large cups (CDR \geq 0.65). Statistical analysis was done using SPSS vs.20 software. Multivariate analysis was used to test the ethnicity and age influences on the measurements. Differences between groups were assessed using ANOVA and ANCOVA analysis. A p-value of less than 0.05 was considered statistically significant.

5.5 Results

5.5.1 NRR thickness: Mean values

When considering discs with cups of all sizes, the nasal NRR was found to have the thickest rim followed by the inferior, superior and temporal rim. The temporal rim was significantly thinner than the other four rim sectors. The NRR thicknesses were normally distributed with a greater spread of values in the nasal sector. The average NRR thickness for all 298 eyes is shown below in table 5.1.

Table 5.1: Mean NRR thicknesses (all eyes) n=298

NRR Sector	Mean value (mm)	SD
Inferior	0.536	0.104
Superior	0.473	0.110
Nasal	0.587	0.135
Temporal	0.353	0.935

5.5.2 Disc size and shape: Influence on NRR thickness

Vertical disc ovality showed significant positive correlations with the inferior and superior NRR thickness ($p=0.003$ and $p=0.001$) and a negative correlation with NRR area ($p=0.006$) and nasal NRR thickness ($p<0.0001$) but not with the temporal NRR thickness. The results show that increasingly oval discs exhibit thicker inferior and superior NRRs and thinner nasal NRRs (table 5.2).

Table 5.2 Disc size and shape: Influence on NRR thickness (Pearson's r)

	Vertical Disc Diameter	Horizontal disc diameter	Disc Area	Disc Ovality
NRR Area	$r=0.669$ $p<0.0001^*$	$r=0.700$ $p<0.0001^*$	$r=0.789$ $p<0.0001^*$	$r=-0.149$ $p=0.006^*$
Inferior NRR	$r=0.171$ $p=0.001^*$	$r=0.025$ $p=0.648$	$r=0.106$ $p=0.047$	$r=0.157$ $p=0.003^*$
Superior NRR	$r=0.054$ $p=0.320$	$r=-0.086$ $p=0.108$	$r=-0.019$ $p=0.729$	$r=0.171$ $p=0.001^*$
Nasal NRR	$r=0.099$ $p=0.066$	$r=0.263$ $p<0.0001^*$	$r=0.220$ $p<0.0001^*$	$r=-0.219$ $p<0.0001^*$
Temporal NRR	$r=-0.43$ $p=0.423$	$r=0.016$ $p=0.767$	$r=-0.015$ $p=0.774$	$r=-0.074$ $p=0.171$

*Significant correlations at $p<0.05$

Disc size is positively correlated with NRR area, but poorly correlated with inferior and superior NRR thickness. Vertical disc diameter was positively correlated with inferior NRR thickness ($p=0.001$) and horizontal disc diameter was positively correlated with NRR thickness ($p<0.0001$).

PPA: There was no statistically significant relationship between disc size, cupping or NRR thickness and PPA for normal eyes at $p<0.05$.

5.5.3 Adherence to the “ISNT” rule

Each ONH image was analysed for adherence to the ISNT rule and for each portion of the ISNT rule using the NRR thicknesses for each sector at the 12, 3, 6 and 9 o'clock positions. The results found that 5.7% of eyes obeyed the ISNT rule, 75.9% of eyes had a thicker inferior than superior rim, 14.4% of eyes had a thicker superior than nasal rim and 98% of eyes had a thicker temporal than nasal rim. Overall, 74.6% of eyes obeyed the thickness pattern of inferior> superior> temporal NRR thickness, compared with only 5.7% which obeyed the inferior> superior> nasal> temporal pattern.

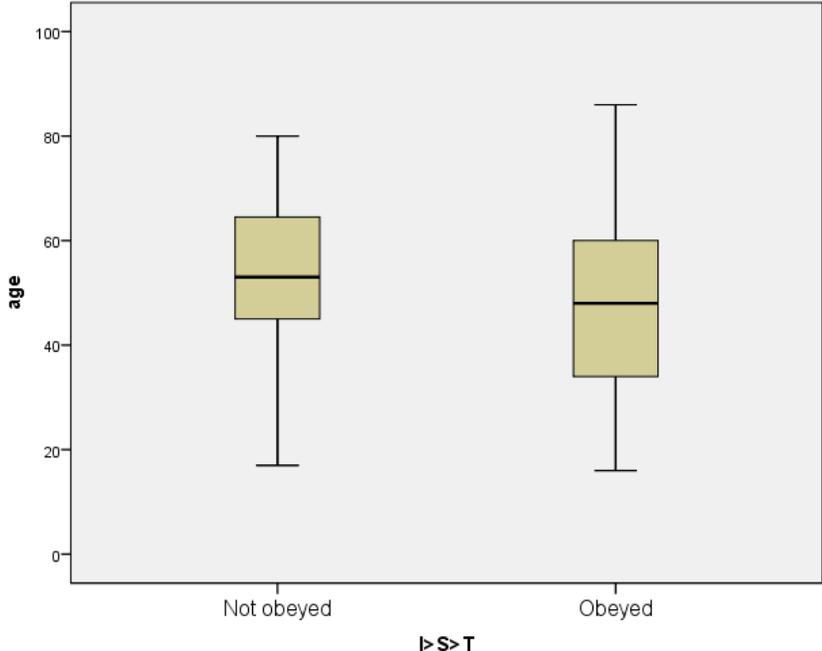
5.5.4 Influence of ocular and systemic factors on obeying the ISNT rule

Regression analysis and Anova were used to investigate influences on obeying the ISNT rule.

5.5.4.1 Age

Simple correlation found that obeying both the ISNT and IST rule decreased with age ($r=-0.157$, $p<0.01$ and $r=-0.173$, $p<0.01$), due to the inferior:superior rim ratio decreasing with age ($r=-0.155$ $p=0.07$). Forward stepwise multiple regression confirmed that age had a negative influence on the inferior>superior rim ratio ($\beta=0.164$, $p=0.004$) and on obeying the I>S>T rule ($\beta=-0.181$, $p=0.002$), but had no influence on obeying the ISNT rule.

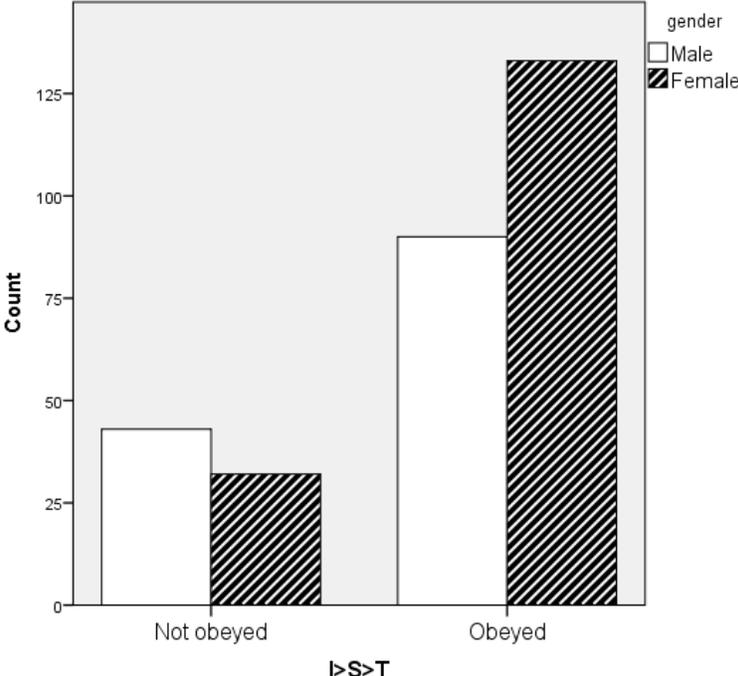
Figure 5.1: Influence of age on obeying the I>S>T rule (n=298)



5.5.4.2 Gender

Females were more likely to obey the IST rule than males (r=0.148 p=0.01) due to a greater inferior>superior rim ratio (r=0.132 p=0.023).

Figure 5.2 Influence of gender on obeying the I>S>T rule (n=298)



5.5.4.3 Disc Size and Shape

Simple correlation found increased disc ovality was associated with obeying the ISNT rule ($r=0.254$ $p<0.0001$) and an increased superior:nasal NRR ratio ($r=0.290$ $p<0.0001$). These finding was confirmed by multiple regression ($\beta=0.301$, $p<0.0001$, ($\beta=-0.194$, $p<0.0001$). Disc ovality does not influence obeying the IST rule ($p>0.05$).

A Multiple regression analysis found disc area to have a postive influence on the inferior:superior rim ratio ($\beta=0.138$, $p=0.017$) and obeying the IST rule ($\beta=0.142$, $p=0.014$).

5.5.4.4 Ethnicity

The rim thickness was investigated in the two ethnic groups, as previous chapters have found differences in disc shape between the two ethnic groups. This data considers discs with a CDR greater than 0.2. The data was analysed for all ages and the glaucoma screening population (≥ 40 years).

Table 5.3: Neuroretinal rim (NRR) thickness: Ethnic differences: All ages n=298

NRR Sector	WE [†] : Mean thickness ±SD (n = 216)	SA [†] : Mean thickness ±SD (n = 82)	Difference and p values (t-test)
Inferior	0.543 ± 0.105	0.518 ± 0.099	0.025, p=0.062
Superior	0.483 ± 0.113	0.447 ± 0.095	0.037, p=0.010*
Nasal	0.606 ± 0.141	0.539 ± 0.103	0.067, p=0.0001*
Temporal	0.366 ± 0.096	0.321 ± 0.077	0.045, p=0.0002*

[†] WE = White European SA = South Asian

*significant at $p<0.05$

Table 5.4: NRR thickness: Ethnic differences: ≥ 40 years

NRR Sector	WE [†] : Mean thickness ±SD (n = 175)	SA [†] : Mean thickness ±SD (n = 36)	Difference and p values (t-test)
Inferior	0.587 ± 0.149	0.561 ± 0.127	0.026, p=0.330
Superior	0.543 ± 0.170	0.497 ± 0.145	0.046, p=0.132
Nasal	0.634 ± 0.147	0.573 ± 0.114	0.061, p=0.020*
Temporal	0.433 ± 0.177	0.375 ± 0.141	0.058 p=0.066

[†] WE =White European SA = South Asian

*significant at $p<0.05$

The SA population showed significantly thinner superior, temporal and nasal NRR thicknesses compared with the WE group (all ages). There was no statistical difference in inferior NRR thickness between the two ethnic groups. However only the nasal NRR thickness remained significantly different in the over 40 age group (p=0.020).

The ISNT rule was investigated in the two ethnic groups; the results are shown in table 5.5 and show a larger adherence to the ISNT rule in the SA group.

Table 5.5: Ethnic differences and adherence to the ISNT rule (all ages)

	WE [†] eyes obeying n=216	SA [†] eyes obeying n=82
Obeys ISNT rule	9 (4.12%)	9 (10.98%)
Inferior > Superior	161 (74.54%)	66 (80.49%)
Superior > Nasal	28 (12.95%)	15 (18.2%)
Nasal > Temporal	213 (98.6%)	80 (97.55%)
Inf > Sup > Temp	158 (73.15)	65 (79.27%)

[†] WE = White European SA = South Asian

The ethnic differences were investigated in an Ancova model and found no differences between the two groups when corrected for age and gender (p>0.05). The glaucoma screening population (over 40 years of age) was also investigated for adherence to the ISNT rule; the results are shown in table 5.6. Multiple regression corrected for gender also confirmed no difference between the two ethnic groups in either obeying the ISNT or IST rule (p>0.05) despite the NRR differences between the two groups.

Table 5.6: Ethnic differences and adherence to the ISNT rule: over 40 years

	WE [†] Eyes obeying n=175	SA [†] eyes obeying n=36
Obeys ISNT rule	7 (4%)	2 (5.6%)
Inferior > Superior	124 (70.9%)	27 (75%)
Superior > Nasal	25 (14.3%)	4 (11.1%)
Nasal > Temporal	172 (98.3%)	35 (97.2%)
Inf > Sup > Temp	121 (69.1%)	26 (72.2%)

[†] WE = White European SA = South Asian

5.5.5 Influence of CDR on obeying the ISNT rule

The discs were subdivided into small cups (CDR 0.2-0.4), medium cups (CDR 0.45-0.6) and large cups (CDR ≥0.65). Ancova analysis (corrected for age and gender) found that larger cups were more likely to obey the ISNT rule and have a greater superior:nasal NRR ratio than smaller cups. Cup size did not have any influence on obeying the IST rule (p>0.05). The results are shown in table 5.7.

Table 5.7: Influence of cup size on obeying the ISNT rule (actual numbers of eyes shown together with % of eyes in each cup group)

	Small cup (n=100)	Medium cup (n=165)	Large cup (n=23)	ANCOVA Corrected for age/gender
Obeys ISNT	6 (5.5%)	7 (4.2%)	5 (11.5%)	p=0.004*
Inf>Sup	78 (70.9%)	132 (80%)	17 (73.9%)	p=0.212
Sup>Nasal	12 (10.9%)	22 (13.3%)	9 (39%)	p=0.002*
Nasal>Temp	108 (98.2%)	163 (98.8%)	22 (95.7%)	p=0.548
Inf>Sup>Temp	76 (69.9%)	131 (79.4%)	16 (69.6%)	p=0.124

*significant at $p < 0.05$

5.6 Discussion

5.6.1 Main findings

The majority of discs did not obey the ISNT rule (94.3%) due to a larger nasal NRR than superior rim. In contrast, removing the nasal NRR from the rule resulted in 74.6% of eyes obeying the IST rule. As the ONH increased in vertical ovality (more common in the SA group), the nasal NRR rim became thinner resulting in a higher number of eyes obeying the ISNT rule. The IST rule was less affected by disc shape and ethnicity than the ISNT rule making it more suitable for use in a multi-ethnic clinical setting. As age increased, the inferior:superior NRR ratio decreased resulting in fewer eyes in the older age group obeying both the ISNT and IST rule. Obeying the IST rule was not influenced by cup size in the current study.

5.6.2 Adherence to the ISNT rule

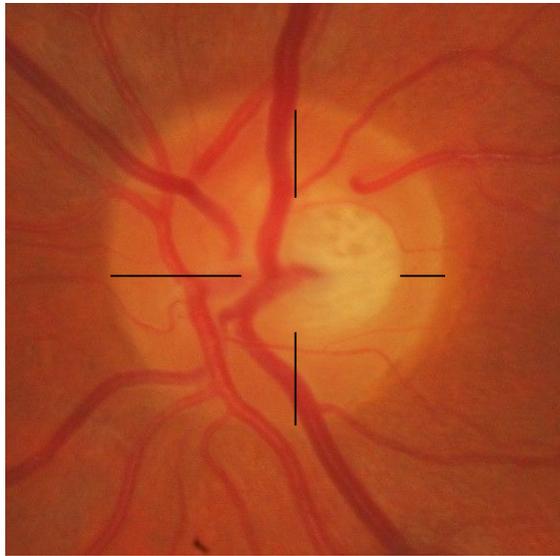
Knowledge of the NRR configuration of the ONH in the normal population and the factors affecting it, is essential when assessing the ONH for glaucoma. The ISNT rule has been rapidly adopted into clinical practice since the NRR distribution was first presented (Jonas et al 1988). However this is an index of normality and the percentage of eyes with early glaucoma that obey the rule was not considered.

The current study aimed to evaluate the ISNT rule and breakdown its I>S>N>T ratios to determine the pattern in the normal population as measured by planimetry. This is arguably the most relevant method to clinical practice, in which the ONH is quickly assessed by ophthalmoscopy for adherence to the rule. In addition, the role of disc shape and size, cupping, ethnicity, gender and age were all evaluated to assess their influence

on the NRR ratios. To the authors knowledge this has not been previously assessed in a single study.

The nasal NRR was found to have the thickest NRR (0.587 ± 0.135) followed by the inferior (0.536 ± 0.104), superior (0.473 ± 0.110) and temporal NRR (0.353 ± 0.935). Many published papers report either the inferior rim to be the thickest (Jonas et al 1988, Pogrebrinak et al 2009), or similar thicknesses for the inferior, superior and nasal rim (Jonas et al 2003, lester et al 2011). An Indian study found the nasal rim to be thicker than the superior rim (Arvind et al 2008). Many studies have however, simply reported if the ISNT rule is obeyed or not obeyed rather than a breakdown of the sector NRR ratios. It is likely that assessment of the NRR edge by planimetry will be thicker than by computerised methods which can more accurately identify the nasal cup edge. However the essence of the ISNT rule is that it is a quick check by ophthalmoscopy in a clinical setting and in this respect although planimetry may be less accurate, it is more comparable to ophthalmoscopy.

Figure 5.4: Disc typically not obeying the ISNT rule but obeying the IST rule



The ISNT rule was found to be obeyed by only 5.7% of normal eyes, this increased to 11.% in the SA group, this difference is likely to be caused by the small sample of eyes obeying the ISNT rule. This observation is lower than many reported studies due to the nasal NRR being thicker. The other aspects of the ISNT rule were obeyed by the majority of eyes, with inferior>superior being obeyed by 75.9% of eyes and temporal>nasal being obeyed by 98% of eyes. Only 14.4% of eyes obeyed the superior>nasal rule.

The nasal NRR rim is difficult to identify by observation due to the retinal vessel trunk which usually exits the optic nerve in the nasal sector, although the actual position of the retinal trunk varies between eyes. The nasal NRR is easily identified by HRT as it uses 3D

imaging; this is not however, comparable with direct observation of the disc. Locating the nasal cup edge accurately is difficult this has also been reported in other studies (Arvind et al 2008), the nasal NRR is also the last to be affected by glaucoma. Due to these factors, the nasal sector was removed from the analysis in a separate assessment of the I>S>T rule rather than the I>S>N>T rule. The idea of removing the nasal sector was also suggested previously (Sihota et al 2007). In the current study, removing the nasal sector resulted in 74.6% of eyes obeying the IST rule.

5.6.3 The Influence of disc and cup size and shape on obeying the ISNT and IST rules.

The disc shape has been little considered with regard to the ISNT rule. Jonas found that greater vertical disc diameters were associated with higher inferior: temporal ratios and higher superior: temporal ratios (Jonas et al 2003). It has also been found that increased vertical disc diameters are associated with a broken ISNT rule (Lundmark et al 2010), however only the diameter was considered, not the shape.

Discs with greater vertical ovality in the current study, were found to be more likely to obey the ISNT rule due to an increased superior: nasal NRR ratio. The SA group were found in previous chapters to have more vertically oval discs and in this part of the study were found to be more likely to obey the ISNT rule than the EW group. However, after Ancova analysis, there was no association with ethnicity and obeying the ISNT rule, indicating that that the NRR ratios are preserved in differing disc shapes. There was no association with either ethnicity or disc ovality and obeying the IST rule, as the nasal sector had been removed from the analysis (the nasal NRR tended to reduce in thickness as the ovality increased). The use of the IST rule therefore is more suitable for all disc shapes compared with the ISNT rule and more appropriate when assessing mixed ethnic groups.

Several studies have indicated that as the CDR increases, the disc is less likely to obey the ISNT rule (Jonas et al 2008, Pogrebniak et al 2009). This is contra to the idea of using the ISNT rule for glaucoma screening, as the suspicion of glaucoma increases as the CDR increases and if larger CDRs are less likely to obey the ISNT rule in normal eyes, this makes the rule of little help in glaucoma screening. The current study found that larger CDRs were more likely to obey the ISNT rule but not the IST rule, due to an increased superior: nasal NRR ratio. The results show that the IST rule can therefore be applied to discs of any shape or CDR and vindicates its possible use in screening. There was a weak association with increasing disc area and obeying the IST rule due to an increased inferior: superior NRR ratio.

5.6.4 The Influence of non-ocular factors on obeying the ISNT and IST rules.

There are very few reports in the literature on the influence of age, ethnicity and gender and the ISNT rule. Lundmark et al (2010) found no influence by age or gender on obeying the ISNT rule, the sample sizes were however small (n=177) and the disc shape was not considered. The current study found that with increasing age, the ratio of the inferior: superior NRR ratio decreased resulting in a decrease in obeying the IST rule with age, this was highly significant. Females were also found to be more likely to obey the IST rule than males. The SA group were slightly more likely to obey the ISNT rule than the WE group, but no more likely to obey the IST rule. This suggests that despite the differing disc shapes and NRR thicknesses of the two groups, the IST rule can be equally applied to both.

5.6.5 Clinical Relevance

This study highlights the dangers of over-reliance on the ISNT rule in a clinical setting. The findings support the use of the IST rule rather than the ISNT rule when assessing the disc for normality. The IST rule removes the problems of assessing the nasal cup margin and removes the effects of ethnicity and disc shape as factors on obeying the rule. In a separate study into inter-eye differences (see appendix 6), left eyes were found to have thicker nasal NRRs than right eyes, laterality may therefore be important when assessing a disc for the ISNT rule, but not the IST rule.

The IST rule is therefore more appropriate for assessing normality in a mixed ethnic, clinical setting and can be applied equally to discs of all CDRs. It is also helpful to know that increasing age and to a lesser extent male gender and smaller discs are associated with a reduced adherence to the rule.

It is possible that these findings could be incorporated into a decision tree analysis for use in a clinical setting to assess which patients might benefit most from addition tests such as visual fields or HRT. This idea will be further explored in chapter 8.

5.6.5 Study Limitations

All the images were assessed and measured by eye using planimetry which is regarded as less accurate than computerised image analysis using OCT and HRT. The location of the cup edge was assessed subjectively three times and the average taken to reduce errors, it was often difficult to judge the cup margin, particularly in the nasal sector, however this mirrors the problems faced by the clinician in a practice setting. The study was also limited by the low number of eyes that obeyed the ISNT rule which presented problems with the statistics, ideally a larger sample size of eyes that obey the ISNT rule is

required to assess influencing factors. This study only considered normal eyes and cannot therefore comment on the use of the 1ST rule in glaucoma screening. Further study is needed using eyes with early glaucoma.

Chapter 6

Summary and Conclusions

6.1 Summary

Early detection of glaucoma requires careful evaluation of the optic nerve head, in combination with IOP and visual field measurements. Due to the wide variation in the ONH appearance, early glaucomatous changes can be easily missed. The ONH has been studied extensively in the literature but studies of ethnic differences are often concerned with only a small area of investigation and do not bring together all the possible influencing factors. In the UK, the largest ethnic minority is south Asian (predominantly Pakistani and Indian), no study has sought to address any ONH differences in these two groups in the UK. Comparisons can be drawn between Asian and European/American studies but difficulties arise from the use of different methodologies and instruments; as a consequence, the results are often fragmented and contradictory.

The ISNT rule is widely used in practice but lacks evidence based studies to support its use in assessing ONH normality and its role of glaucoma screening. Current studies of the ISNT rule have widely varying results and rarely assess the relative NRR thicknesses in each sector. The influence of disc and cup size and shape is also unclear.

This thesis has been concerned with investigating these areas and introduces a framework of ONH normality intended to assist the optometrist with the intention of improving both the sensitivity and specificity of glaucoma screening in practice.

6.1.1 The influence of Ethnicity on the ONH appearance: South Asian and European White.

The UK today has a diverse multicultural population, the largest ethnic minority being from South Asia (Indian and Pakistan). In the UK there are areas which contain relatively high numbers of people from SA backgrounds. Optometrists in these areas currently carry out glaucoma screening without any knowledge of any ethnic ONH differences between these groups. There is very little in the literature comparing SA and WE groups, most studies involve individual populations or the comparison of white and African ethnic groups.

This thesis intended to address any ONH differences between the SA and WE populations and is, to the author's knowledge the first study to compare these ethnic groups directly in the same study. The results demonstrated no difference in the ONH size between the SA and WE populations, however, independent of age, the SA population showed increased cupping, thinner NRRs and greater CDRs compared with the WE population. Analysis also revealed that the SA population had a more vertically oval disc shape compared with the WE population, resulting in proportionally thicker superior and inferior NRR's. These findings have not been previously reported. This suggests that care should be taken when assessing SA discs, as a vertically enlarged cup, one of the signs

of glaucoma, could be interpreted as normal in a vertically oval disc; vertical enlargement of the cup in rounder WE discs are likely to be easier to detect. No differences were found between the two ethnic groups with regard to inter-ocular differences, PPA or obeying the IST rule.

The upper limit of CDR asymmetry is often quoted as 0.2 (Jonas et al 1988), which is in agreement with this study for both ethnic groups. The two eyes of an individual were highly correlated with the majority of subjects showing a CDR of ≤ 0.1 difference and an average 1mmHg difference in IOP, there was no statistical differences between the ethnic groups with regards to inter-eye asymmetry.; the upper limits of normality were CDR: 0.2 and IOP: 3mmHg (mean \pm 2SD). These upper limits can be applied to patients from both the SA and WE ethnic groups.

Conclusions

- The SA and WE populations show no difference in ONH size.
- The SA population demonstrates greater cupping and CDRs and thinner NRRs than the WE population.
- The SA population have ONHs that are more vertically oval in shape with proportionally thicker superior and inferior NRRs than the WE population whose ONHs tend to be rounder in shape.
- Both ethnic groups show similar amounts of inter-eye asymmetry.

6.1.2. The ISNT rule

The ISNT rule is an example of a normal observation being adopted into clinical practice in the absence of any clinically based evidence to support its use in glaucoma screening. The use of the ISNT rule is so ingrained in optometry, that its use is almost universally accepted; however recent studies have found not only variable numbers of normal eyes obeying the rule (table 5.1), but that its use in glaucoma screening is limited (Morgan et al 2012).

This research sought to investigate the ISNT rule in the normal population and to determine any influencing factors with regard to the distribution of NRR thickness. The findings of this study support the use of the ISNT rule with the nasal sector removed to become the IST rule. This study found only 5.7% of normal eyes obeying the ISNT rule due to only 14.4% of eyes obeying the superior>nasal part of the rule. The nasal NRR was found to be the thickest NRR in the majority of eyes and to show the most variability. Removing the nasal sector from the rule resulted in 74.6% of eyes obeying the IST rule, which also proved independent of ethnicity and disc size and shape and cup size. The

glaucoma screening population (≥ 40 years) were found to be less likely to obey the ISNT and IST rule due to a decreased inferior: superior NRR ratio. Larger discs and female gender were found to be more likely to obey the IST rule.

Conclusions

- The ISNT rule is only obeyed by a minority of normal eyes (5.7%) compared with the number of eyes that obey the IST rule (74.6%).
- Vertically oval discs are more likely to obey the ISNT rule due to a thinner nasal NRR.
- Age is associated with a reduction in obeying both the ISNT and IST rule due to a greater inferior: superior NRR ratio.
- Obeying the IST rule is not associated with cup size or disc shape.
- This research supports the use of the IST rule rather than ISNT rule for assessing NRR thickness normality.

6.2 Clinical Implications arising from this work

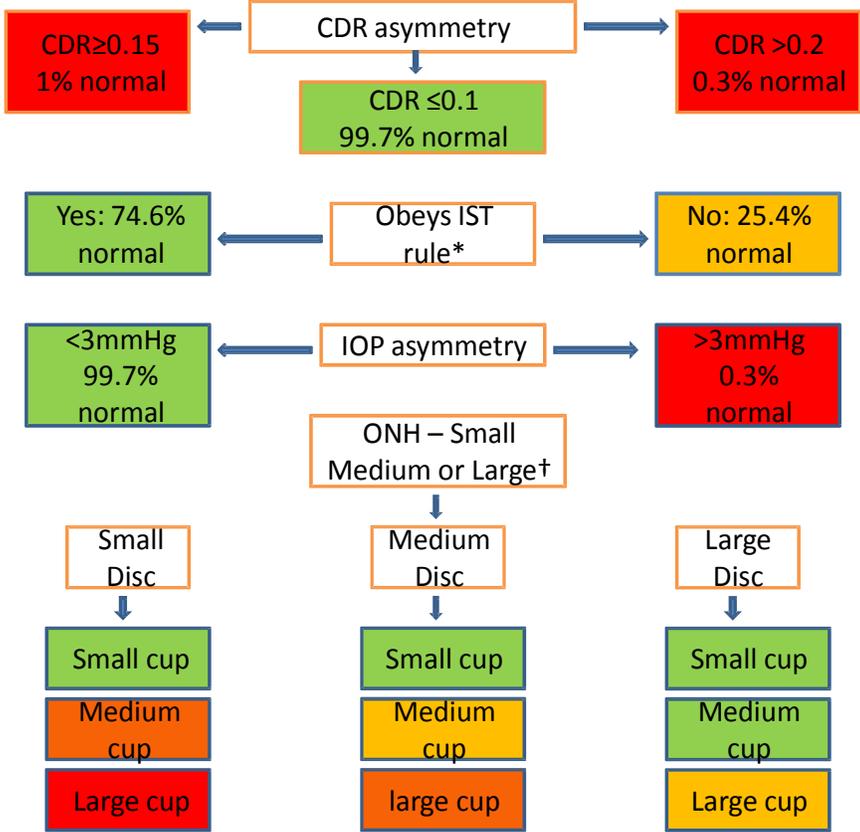
The main implications are:

- Identification of ethnic ONH differences and similarities between the SA and WE groups and the knowledge that the upper limits of inter-eye differences are valid for both ethnic groups. The SA population demonstrate larger cupping, thinner NRRs and a more vertically oval disc shape compared with the WE population but show no difference in disc size.
- Less reliance should be placed on the ISNT rule in practice and it should be replaced by the IST rule when assessing normality. The IST rule can be applied to discs of all shapes and sizes and is valid for both ethnic groups. Even so, 25% of normal eyes still do not obey the IST rule and other cues should also be used when assessing the disc.

The framework proposed (figure 6.1) is intended as a guide to help the optometrist assess a disc for normality as an alternative the widely used ISNT rule. No guide to normality can aim to be used in isolation or be a replacement for other cues such as disc haemorrhage, bayoneting, focal NRR loss etc. But can be applied to a disc without these signs, to predict the likelihood of normality and to identify those patients that would benefit from further tests such as VF testing. This proposal could be incorporated into a computer based application (app) for use in the consulting room, or into a computerised visual field screener to combine ONH and VF data to help predict normality.

The framework indicates the likelihood of normality with green indicating that the disc is likely to be normal, amber is suspicious and red unlikely to be normal. Patients with green scores with regard to IOP and disc asymmetry and cupping are highly likely to be normal. Patients with one or more amber scores will require further investigation such as VF testing. Red scores indicate a high likelihood of abnormality. Additional factors could be added to the framework, including disc shape and cup shape which are known from this study to be influenced by ethnicity and gender. Cup shape, in particularly vertical cupping should be assessed independently of the disc shape.

Figure 6.1: Framework for assessing ONH normality



* Greater likelihood of obeying in females, <40 years and large discs

† Larger cupping in the SA group compared with the WE group

6.3 Study Limitations

The recruitment method involved the reliance of patient selection by practice staff, this was not always done at busy periods; some unsuitable patients were also recruited who

had to be removed from the study. These disadvantages were however, considered to be small compared to the advantage of the random nature of participant selection from the optometric population, a criticism directed at some other studies in a review article by Jonas et al (1999). It is also accepted that the accuracy of the ONH planimetry would have benefitted from stereoscopic viewing, however this was not available. Analysis of all the images was done by a single observer and is comparable to direct ophthalmoscopy, it is likely that any over or underestimation of cup and disc margin would cancel out across all the images.

The patient history with regards to their health and medication was limited due to the self reporting nature of the information and lack of any medical records, due to these problems, it is accepted that some errors will occur, this limited the usefulness of the BP and migraine analysis but also reflects the difficulty in screening the general population in the absence of their medical records.

6.4 Future areas of research arising from this work

This research has concentrated on the normal optic nerve head and as such provides a framework for normality. It cannot assess the specificity or sensitivity of glaucoma screening as no patients with glaucoma were included in this study. Future research assessing both the usefulness of the framework and its impact on glaucoma screening would address this. The usefulness of the IST rule compared with the ISNT rule also needs to be addressed in glaucoma screening, as the number of glaucomatous eyes that obey the IST rule is unknown. Only if the IST rule proves useful in detecting glaucoma from normal eyes should its use be implemented into practice.

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Appendix 1: Ethical approval

Response from AOREC

11th January 2010

Project title: Evaluation of the optic disc parameters in a normal population in a daily optometric practice: Effect of age, refractive error, intraocular pressure and ethnicity.

Reference Number: Collin OD

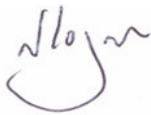
Researchers: Dr Doina Gherghel and Mrs Catherine Collin

I am pleased to inform you that the Audiology / Optometry Research Ethics Committee has approved the above named project.

However on the patient information sheet, under researchers, school and subject area responsible, this should read, 'Optometry, School of Life & Health Sciences, Aston University, Birmingham (unless Aston headed paper is being used).

The details of the investigation will be placed on file. You should notify The Committee of any difficulties experienced by the volunteer subjects, and any significant changes which may be planned for this project in the future.

Yours sincerely



AOREC

Appendix 2: Patient Information Sheet

Patient Information Sheet.

Research Workers, school and subject area responsible

Mrs Catherine Collin, Optometry, school of Life & Health Sciences, Aston University, Birmingham.

Dr Doina Gherghel, Life & Health Sciences, Vision Sciences

Project Title

Evaluation of the optic disc parameters in a normal population in daily optometric practice. Effect of age, refractive error, intraocular pressure, blood pressure and ethnicity.

Invitation

You are being invited to take part in a research study conducted by your optometrist. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

What is the purpose of the study?

The optic nerve at the back of your eye (commonly called the optic disc) varies widely in its appearance with various factors including age, family history of ocular disease, prescription for glasses and even how much blood it gets. The purpose of the study is to build up a profile of the appearance of the optic disc in the normal population. This knowledge will be helpful in the future to determine any risk factors that may exist and subsequently improve screening for glaucoma, a blinding disease that can be often detected in patients coming to their optometrist just for a routine eye exam.

Why have I been chosen?

All patients attending for an eye examination, who do not have glaucoma or high eye pressures or any other eye condition are being invited to take part in this research.

What will happen to me if I take part?

A routine eye examination will be carried out, we simply wish to analyse information and photographs recorded as part of the normal eye examination. In addition to the eye pressure, blood pressure will also be measured. All measurements will be taken on one visit with no further visits required. By volunteering you are giving consent for the optic disc photographs and clinical information to be analysed; this information, however, will be recorded anonymously.

Information to be recorded will include:

- 1 Spectacle prescription
- 2 Age and Gender
- 3 Blood pressure and eye pressure
- 4 Ethnicity
- 5 Family history of glaucoma
- 6 Measurement from the optic nerve photographs
- 7 Any history of ocular and systemic pathology and treatments for such diseases.

The study will be carried out at Specsavers, Unit 4B Cornhill, Accrington, Lancashire, and will be a cross sectional study. Data will be collected for a period of 18 months and no patient follow up is required. If a patient is suspected to be suffering from glaucoma or any other eye disease, they will

be referred to an ophthalmologist for further assessment, in accordance with the College of Optometrist's guidelines. Blood pressure will be also measured during the consultation according to a protocol recommended by the British Hypertension Society; if found to be raised, the patient will be referred to their general practitioner.

Are there any potential risks in taking part in the study?

The eye examination will be carried out in accordance with the College of Optometrists guidelines, which includes patient confidentiality, the data protection act and asking of questions about ethnicity. The association of Optometrists covers clinical indemnity. The only risk in this study is a breach of confidentiality relating to the data collection for this research, this will be minimised by keeping the data anonymous. Mrs C Collin will collect and record the information, any other members of the research team will only have access to the database after your identity has been removed.

Do I have to take part?

No, you do not have to participate if you do not wish to do so. You are free to withdraw at any time from the project without penalty.

Expenses and payments

There are no expenses or payments for participation in this project.

Will my taking part in this study be kept confidential?

Yes, your participation in the study will be fully confidential. Your patient record card will contain no additional information and will be stored as a normal eye examination card. Information for this study will be recorded separately with no personal information. There will be minimal risk of linking the research data to any individual participant. The data will be stored by Catherine Collin on secure computers until the end of the study and then disposed of.

What will happen to the results of the research?

The aim is to publish the findings of this research in professional journals and in a project report/thesis, which will allow other optometrists and health care professionals' access to the results. All information published will be anonymous with no reference to any individual. Details can be obtained from Catherine Collin at the end of this study.

Who is organising and funding the research?

This research is organised by Mrs C Collin as part of a postgraduate research project with Aston University. There is no funding for this project.

Who has reviewed the study?

The proposal was reviewed by Dr Doina Gherghel, Aston University (ophthalmologist and glaucoma specialist) and has been submitted for approval by Aston University's Audiology/Optomety research ethics committee.

Who do I need to contact if something goes wrong or I need further information?

Please feel free to contact Mrs C Collin at the practice in person, telephone or email:

01254 – 395713, collincl@aston.ac.uk.

Who do I contact if I wish to make a complaint about the way in which the research is conducted?

If you have any concerns about the way in which the study has been conducted, then you should contact the secretary of the University Research Ethics Committee on j.g.walter@aston.ac.uk or telephone 0121 204 4665.

Appendix 3: Consent Form

Personal Identification Number for this study: _____

CONSENT FORM

Title of Project:

Evaluation of the optic disc parameters in a normal population in a daily optometric practice: Effect of age, refractive error, intraocular pressure, blood pressure and ethnicity.

Research Venue: Specsavers Opticians, Unit 4B Cornhill, Accrington, Lancashire, England.

Name of Investigator(s):

Principal Investigator: Catherine Collin, Optometrist

Supervisor: Dr Doina Gherghel, Ophthalmologist and Glaucoma specialist

Please initial box

1. I confirm that I have read and understand the information sheet dated (version) for the above study and have had the Opportunity to ask questions. —
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. —
3. I agree to take part in the above study. —

_____ Name of Research Participant	_____ Date	_____ Signature
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_____ Name of Person taking Consent	_____ Date	_____ Signature
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1 copy for research participant; 1 copy for supervisor

Appendix 4: Communication with Professor Jost Jonas

Dear Mrs. Collin,

the ISNT has just gradually been adopted by the clinicians.

Yours sincerely

J. Jonas

----Ursprüngliche Nachricht-----

Von: Collin, Catherine [mailto:collincl@aston.ac.uk]

Gesendet: Freitag, 25. Januar 2013 18:45

An: Jonas, Jost

Cc: Gherghel, Doina

Betreff: RE: The "ISNT" rule

Dear Professor Jonas,

Thank you for your reply, that is really helpful.

I am certainly interested in the clinical usefulness of the ISNT rule. I have collected data in practice from 400 normal patients by assessing optic discs photos and measuring the NRR thickness. I have found differences in the shape of the optic nerve between white and south Asian subjects and I am looking at any differences in the ISNT rule between these two groups (I have found the south Asian group to have more vertically oval discs).

After your original findings in the 1988 paper, I wondered if there was a conference or other publication recommending the use of ISNT rule or if it has just been gradually adopted by clinicians after reading your paper.

Thanks again

Catherine Collin

From: Jonas, Jost [jost.jonas@medma.uni-heidelberg.de]

Sent: 25 January 2013 10:18

To: Collin, Catherine

Subject: AW: The "ISNT" rule

Dear Mrs. Collin,

despite some some clinical research studies, the ISNT rule as qualitative sign is clinically useful for the detection of early glaucomatous changes in the optic disc, since the ISNT rule can be assessed by simple ophthalmoscopy, it takes 5 seconds to examine it, and it picks up early changes in the inferior / or superior disc region, the areas where the early structural loss in glaucoma usually takes place. In morphometric studies by others and also by us, the ISNT rule usually has a low diagnostic precision. If it used as a qualitative

sign (fulfilled or not fulfilled), it can become quite valuable.

Yours sincerely

J. Jonas

-----Ursprüngliche Nachricht-----

Von: Collin, Catherine [mailto:collincl@aston.ac.uk]

Gesendet: Freitag, 25. Januar 2013 11:04

An: Jonas, Jost

Cc: Gherghel, Doina

Betreff: The "ISNT" rule

Dear Professor Jonas,

I am currently studying for an Ophthalmic doctorate at Aston University, Birmingham under the supervision of Dr Doina Gherghel and I would be very grateful for any information related to the "ISNT" rule.

My thesis is titled "The Normal Optic Nerve in an Optometric Population: Correlation with Ocular and Non-Ocular variables". The main areas of my research are:

1. To compare British White and British South Asian optic discs in the normal population (n=400)
2. To investigate inter-eye differences
3. To investigate ocular and non-ocular differences
4. To investigate inter-relating optic nerve parameters
5. To investigate the ISNT rule and its validity in glaucoma screening.

I have read all the papers I can find relating to the ISNT rule, most of which cite your paper from 1988. However I am unsure where the "ISNT" rule has come from as a glaucoma screening tool and how its use became so widespread. I would be very grateful for any information that could provide.

Many thanks,
Catherine Collin

Appendix 5: College of Optometrist Guidelines.

Guideline:B2 The routine eye examination

B2.01 The optometrist has a duty to carry out whatever tests are necessary to determine the patient's needs for vision care as to both sight and health. The exact format and content will be determined by both the practitioner's professional judgement and the minimum legal requirements.

B2.02 The optometrist has a duty to examine patients at the most appropriate intervals in accordance with clinical needs.

Advice

General

B2.03 It is for the practitioner to satisfy him/herself that procedures are included or excluded according to the patient's clinical need.

B2.04 A full examination should include:

(a) Full and accurate collation of patient details. To include name, address, other relevant contact details, date of birth, and relevant details of visual needs, whether occupational, recreational or general (e.g. driving);

(b) Note of reasons for visit, description of onset, character and duration of symptoms, if any, and findings of all tests undertaken;

(c) History: to include any relevant personal or family history of an ocular or general health nature and any medication the patient is taking. Where possible, the patient should be asked to bring details of medication and dosage. Details of previous optical prescription and date of last eye examination or sight test (best estimate if date not known);

(d) The determination of the aided and/or unaided vision of each eye (aided vision should be accompanied by the specific prescription used);

(e) Assessment of habitual ocular muscle balance;

(f) An internal and external examination of the eye (note the requirements of a statutory sight test – see s.B2.19 below). As a minimum this will include direct ophthalmoscopy on the undilated eye. Pupil dilation and/or the use of indirect methods will be appropriate in certain circumstances where an inadequate view of the fundus would otherwise be obtained. Slit-lamp biomicroscopy will be appropriate where a detailed view of the anterior eye and adnexa is required;

(g) Subjective findings to establish visual acuity of each eye individually.

B2.05 In addition to the procedures above a full examination may include:

(a) An assessment of the patient's visual needs and visual environments;

(b) Ocular motility assessment, convergence, pupil reflexes;

(c) Visual field assessment on all relevant patients, especially those at risk of glaucoma.

(See section D3 on Examining the patient at risk from glaucoma);

(d) Objective refractive findings;

(e) Binocular balancing and binocular visual acuity as appropriate;

(f) Assessment of accommodation to determine any additions to the distance prescription, if required for intermediate or near tasks;

(g) Intraocular pressure measurement on patients at risk of glaucoma.

(See section D2 on Examining the patient at risk from glaucoma).

B2.06 On completion of all appropriate tests, suitable advice on the findings should be given to the patient and the patient advised when to re-attend for their next routine eye examination.

B2.07 The practitioner should conduct an examination that is appropriate to the immediate needs of the patient. The optometrist may need to justify his/her actions subsequently so that when a test that would otherwise be considered necessary for that patient cannot be carried out, the optometrist should record the reason for this on the patient record card. Please note the required elements of a statutory sight test (see paras B2.19 and B2.20).

B2.08 It is very important to record all findings accurately during the examination. If findings are not recorded, it cannot be assumed that the relevant test has actually been carried out. (See section A9 on Patient records).

B2.09 It should always be made clear to the patient in advance whether the examination will be carried out under the NHS or privately. Any payments for procedures in addition to the sight test should be agreed with patients in advance.

Required content of statutory sight test

B2.19 s 36(2) of the Opticians Act states that:

“References in this Act to testing of sight are references to testing sight with the object of determining whether there is any and, if so, what defect of sight and of correcting, remedying or relieving any such defect of an anatomical or physiological nature by means of an optical appliance prescribed on the basis of the determination”. The regulatory background to the eye examination (whether performed privately or under the GOS) is contained in the Sight Testing (Examination and Prescription)(Number 2) Regulations, which were made in 1989, as a result of measures contained in the Health & Medicines Act 1989.

B2.20 The essential words relating to the sight test are these:

(1) When a doctor or optician tests the sight of another person, it shall be his duty (a) to perform, for the purpose of detecting signs of injury, disease or abnormality in the eye or elsewhere

(i) an examination of the external surface of the eye and its immediate vicinity,

(ii) an intra-ocular examination, either by means of an ophthalmoscope or by such other means as the doctor or optician considers appropriate,

(iii) such additional examinations as appear to the doctor or optician to be clinically necessary

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B2.21 These Regulations also contain provisions relating to:

- the duty to issue a prescription or statement;
- exceptions to that duty;
- the particulars to be issued in a prescription or statement.

NHS regulations

Fees

B2.22 The College endorses the need for fees to reflect the professional service provided. Nothing in this guidance prevents the optometrist from making appropriate charges for procedures. However, where a sight test is funded by the NHS, practitioners are reminded that it is a breach of regulations to charge for any procedure undertaken as part of a GOS sight test in England, Northern Ireland, Scotland and Wales.

Necessity of sight testing

B2.23 In England, the National Health Service General Ophthalmic Services Contracts Regulations 2008 require practitioners to satisfy themselves that a sight test is necessary. Similar provisions apply in Northern Ireland, Scotland and Wales.

Patients with diabetes and glaucoma

B2.24 In England, the National Health Service General Ophthalmic Services Contracts Regulations 2008 require that every time the optometrist ‘tests the sight’ of a patient diagnosed as suffering from diabetes or glaucoma, s/he must inform the patient’s doctor or GMP practice of the results of the test. Similar provisions apply in Northern Ireland, Scotland and Wales.

Equality Act 2010

B2.25 The Equality Act determines that everyone has the right to be treated equally and individuals are protected from unfair treatment. It makes it unlawful to discriminate, directly or indirectly, against people by virtue of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation. In particular service providers have to make ‘reasonable’ adjustments to their practice environment and fabric to ensure that disabled people can access their services.

Appendix 6: Inter-ocular differences in optic nerve head topography in normal subjects

Abstract

Purpose: This study aimed to determine inter-ocular differences in the optic nerve head appearance as assessed by fundus photography in the normal population to provide a framework to assist in glaucoma screening.

Methods: An optometry based cross sectional study was carried out in North West England between February 2010 and February 2011. 296 White European and 100 South Asian participants were recruited to the study. All patients underwent retinal photography, refraction and, intra-ocular pressure measurements. Optic nerve morphology was assessed using computer aided analysis. The inter-ocular differences were compared as a whole group, as ethnic groups and age groups; correlations with IOP were also investigated.

Results: There was no statistically significant differences between the two eyes with regard to IOP and refraction ($p>0.05$). In addition, NRR area also showed no difference between right and left eyes ($p>0.05$). However, independent of age, gender, ethnicity and FH of glaucoma, right eyes showed thinner nasal NRRs ($p=0.042$) and significantly smaller vertical cup diameters in right eyes ($p=0.03$) compared with left eyes. When considering subjects ≥ 40 years, no difference between right and left eyes were found ($p>0.05$); when inter-ocular ONH asymmetry was compared to the under 40 age group, no statistical differences were found ($p>0.05$). Subjects <40 years did however show an increased degree of IOP asymmetry ($p=0.0036$) compared with the ≥ 40 years group. No significant correlations were found between ONH asymmetry and IOP asymmetry.

Conclusion: Results indicate a displacement of the cup between right and left eyes, this is important when assessing the NRR thickness between fellow eyes. The over 40 years age group showed less IOP asymmetry than the younger age group. The CDR area ratio appears to be a good measure of assessing ONH asymmetry. There are no differences in inter-ocular asymmetry with age or ethnicity. Upper limits of inter-ocular asymmetry in this study were an IOP difference of 3mmHg and a CDR area ratio of ≤ 0.2 .

Introduction

Differences in the ONH between the two eyes of the same patient are important when screening for glaucoma. Glaucoma is an asymmetric disease and one of the first indicators of early glaucoma is an enlargement of the optic cup in the affected eye resulting in asymmetrical cupping. Knowledge of the degree of asymmetry both of the ONH and the IOP within the normal population is important when screening for glaucoma. The use of the CDR to document the ONH in glaucoma screening was first described by Armaly in 1969 and despite its shortcomings, is still widely used in optometric practice. It is also important to investigate inter-eye differences when considering studies into the optic nerve head. Studies often take one of two approaches:

- 1: To randomly select one eye from each subject, or use all right or all left eyes.
- 2: To use all eyes to increase the data size and apply statistical methods to correct for inter-eye similarities, such as that used by Ramrattan (1999).

However it must be questioned if all inter-eye differences are the same for all variables and groups of patients. Published data on intraocular differences varies widely. Several studies have found intraocular differences in the RNFL, however some studies show thicker values in left eyes using the HRT (Gherghel et al 2000) and some thicker values in right eyes using the OCT (Mwanza et al 2010). Most studies have found no difference in laterality between any of the ONH parameters (Durukan et al 2004, Herman et al 2004, Vernon et al 2005, Gherghel et al 2000). The IOP difference between eyes is also important and a higher pressure in one eye will alert the clinician to possible glaucoma, particularly if the affected eye has a larger CDR. Although an IOP >21mmHg is regarded with suspicion and grounds for referral by an optometrist to an ophthalmologist (NICE guidelines 2011), the IOP inter-ocular difference that is normal is less clear especially when both eyes are under 21mmHg. This study will address both the optic disc differences and the IOP differences to determine any correlation.

Study aims

This study aims to provide a profile of the inter-eye differences in optic disc parameters in the normal population and their possible relationship with the inter-ocular differences in IOP.

Subjects and Methods

Recruitment of participants

Patients free from optic nerve disease were recruited to this study as they attended for an optometric eye examination in a high street practice. Main exclusions are given in section 2.1.1. In addition, subjects with only one image were excluded and patients with anisometropia over 2.00D were also excluded from this part of the study.

Ethics approval

Ethical approval was obtained from the Aston University ethics approval committee prior to the start of this study. The study was designed and conducted according to the principles of the Declaration of Helsinki.

Methods

Details of the investigations and methods are given in Chapter 2. Intraocular pressures were measured using the same non-contact tonometer for all patients. Optic disc analysis was carried out using retinal photography and Navis-lite software. Each optic disc was measured three times and the average value used in the analysis.

Statistical Analysis

The inter-ocular difference statistical analysis was performed using paired t-tests.

Unpaired t-tests were used to compare age, gender and ethnic groups. Differences between the ethnic groups were subsequently assessed using ANOVA and ANCOVA. Holms-Bonferroni sequential rejection method was used for significance correction of multiple comparisons. The analysis was carried out using SPSS vs.20.

Results

343 subjects were included in this analysis comprising of: 199 females and 144 males.

Results 1. Intraocular differences: All eyes included

Mean values for the right and left eye ONH parameters are given in table 4.1 together Students t-test p-values. The results are shown in table 4.1.

Table 4.1: Inter-ocular differences, right eye vs. left eyes (n=343)

Parameter	Right Eye Mean ± SD	Left Eye mean ± SD	SQRT [†] (Intereye Difference)± SD	p1- value*	p2- value**
IOP	15.113 ± 2.790	15.067 ± 2.756	0.046 ± 1.376	0.535	NS
V disc area	1.797 ± 0.179	1.812 ± 0.177	0.087 ± 0.083	0.016	NS
H disc area	1.663 ± 0.183	1.668 ± 0.189	0.093 ± 0.094	0.439	NS
Disc area	2.337 ± 0.437	2.372 ± 0.456	0.201 ± 0.208	0.012	NS
V cup diameter*	0.634 ± 0.325	0.664 ± 0.323	0.123 ± 0.129	0.002	0.03***
H cup diameter	0.590 ± 0.311	0.601 ± 0.301	0.122 ± 0.132	0.300	NS
Cup area	0.378 ± 0.267	0.388 ± 0.268	0.100 ± 0.105	0.158	NS
Vertical CDR	0.365 ± 0.168	0.369 ± 0.156	0.068 ± 0.089	0.534	NS
Horizontal CDR	0.359 ± 0.161	0.360 ± 0.154	0.064 ± 0.065	0.760	NS
CDR area	0.166 ± 0.085	0.168 ± 0.086	0.037 ± 0.037	0.368	NS
NRR area	1.961 ± 0.373	1.977 ± 0.400	0.179 ± 0.198	0.253	NS
Inferior NRR	0.591 ± 0.152	0.582 ± 0.145	0.075 ± 0.082	0.050	NS
Superior NRR	0.528 ± 0.171	0.535 ± 0.172	0.073 ± 0.083	0.204	NS
Nasal NRR*	0.608 ± 0.138	0.624 ± 0.138	0.081 ± 0.068	0.003	0.042***
Temporal NRR	0.433 ± 0.180	0.417 ± 0.177	0.077 ± 0.086	0.008	NS

*p1-value: 2 tailed students t-test

**p2-values after Holms-Bonferroni correction

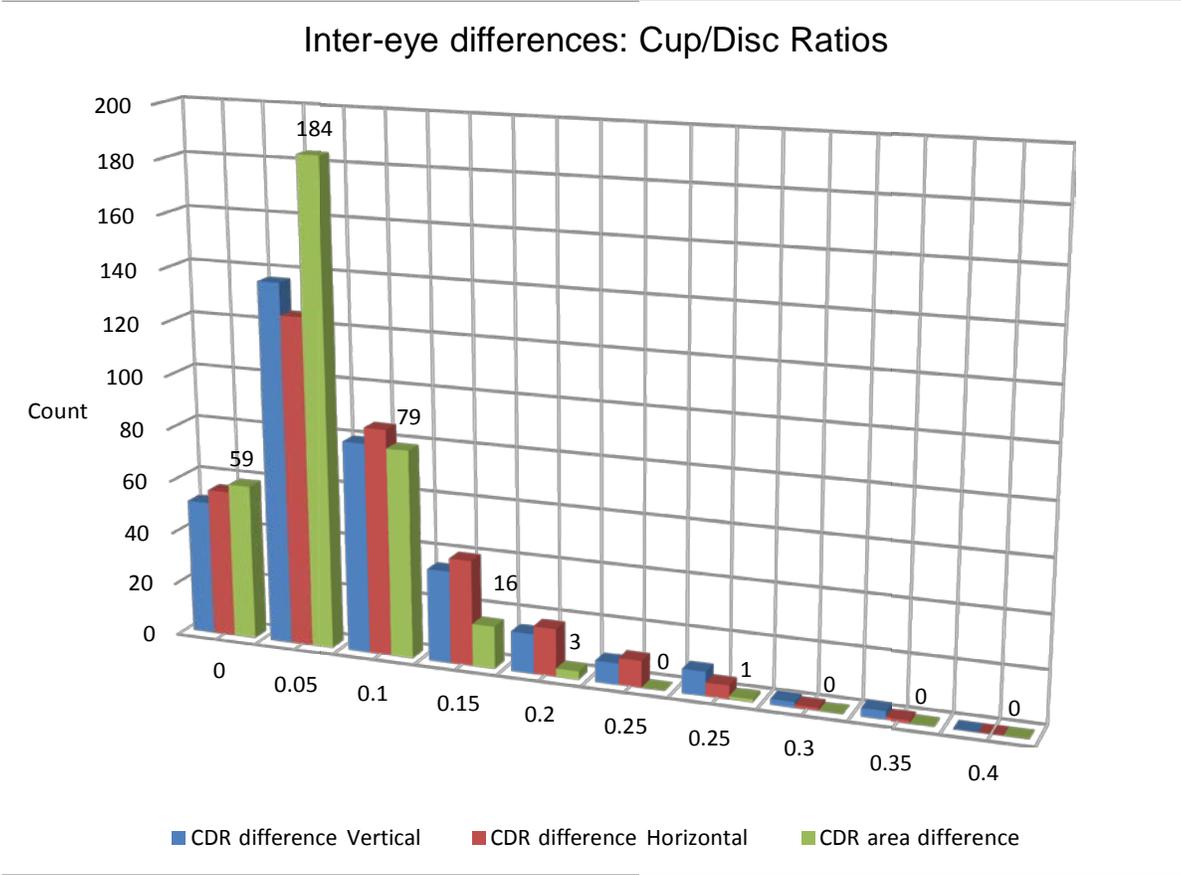
***significant at p<0.05 after Holms-Bonferroni correction for multiple comparisons

SQRT[†] used to remove the sign of the difference

The vertical cup diameter was found to be larger in the left eyes (p<0.05). The nasal NRR thickness was larger in the left eyes compared with right eyes. (p<0.05) However, overall

the NRR area showed no significant difference between eyes. The other ONH parameters showed no preference for side. The vertical CDR was found to vary slightly more within individuals than the horizontal CDR, this was however not clinically significant. In the population examined, subjects showing a CDR area difference of ≤ 0.1 accounted for 73% of subjects, those with a CDR area difference of ≤ 0.15 and ≤ 0.2 accounted for 99% and 99.7% of subjects respectively. No subjects were found to have a CDR area difference of greater than 0.2. The cup to disc distributions are illustrated in figure 4.1.

Figure 4.1: Inter-eye differences, all subjects: Cup/Disc Ratios (n=343)



Results 2. Inter-ocular differences: Results by age group

Glaucoma is more prevalent in the older age group; it is this population that are screened for glaucoma in optometric practice. It is therefore important to know if the normal range for inter-eye differences given in section 4.5.1 applies to the older, glaucoma screening age group. The data was analysed for patients aged ≥ 40 using a 2-tailed student's t-test; no significant differences were found between left and right eyes. The results are given in table 4.2.

Table 4.2: Right eyes vs. Left eyes: Subjects aged ≥ 40 years (n=238)

Parameter	Right Eye Mean \pm SD	Left Eye Mean \pm SD	p-value
IOP	15.142 \pm 2.865	15.055 \pm 2.761	0.736
V disc diameter	1.808 \pm 0.179	1.823 \pm 0.174	0.355
H disc diameter	1.680 \pm 0.187	1.688 \pm 0.190	0.617
Disc area	2.382 \pm 0.444	2.417 \pm 0.459	0.400
V cup diameter	0.631 \pm 0.328	0.664 \pm 0.319	0.261
H cup diameter	0.587 \pm 0.316	0.607 \pm 0.300	0.485
Cup area	0.379 \pm 0.268	0.390 \pm 0.268	0.663
Vertical CDR	0.364 \pm 0.171	0.370 \pm 0.154	0.670
Horizontal CDR	0.355 \pm 0.161	0.360 \pm 0.152	0.771
CDR area	0.165 \pm 0.083	0.167 \pm 0.085	0.748
NRR area	2.005 \pm 0.385	2.017 \pm 0.416	0.735
Inferior NRR	0.595 \pm 0.159	0.584 \pm 0.147	0.436
Superior NRR	0.538 \pm 0.177	0.542 \pm 0.173	0.769
Nasal NRR	0.620 \pm 0.173	0.634 \pm 0.143	0.293
Temporal NRR	0.442 \pm 0.186	0.421 \pm 0.181	0.213

The data was further examined by splitting the subjects into two age groups: < 40 years and ≥ 40 years. Unpaired t-tests were carried out on the inter-ocular differences between each group. The IOP showed increased inter-ocular differences in the younger age group ($p=0.0036$). The NRR area and the nasal NRR thickness showed increased inter-ocular differences in the older age group, but after Bonferroni correction they failed to reach significance, none of the other ocular parameters showed any differences between the two age groups. The results are shown in table 4.3

Table 4.3: Inter-ocular differences: Age

Parameter	<40years inter-eye difference Mean \pm SD (n=105)	\geq 40years inter-eye difference mean \pm SD (n=238)	2 tailed T-test p-value*	p2*
IOP	1.000 \pm 0.953	0.702 \pm 0.524	0.0002	0.0036*
V disc area	0.080 \pm 0.085	0.090 \pm 0.082	0.325	NS
H disc area	0.078 \pm 0.076	0.099 \pm 0.100	0.063	NS
Disc area	0.168 \pm 0.132	0.215 \pm 0.232	0.056	NS
V cup diameter	0.123 \pm 0.135	0.123 \pm 0.127	0.971	NS
H cup diameter	0.116 \pm 0.117	0.124 \pm 0.138	0.589	NS
Cup area	0.087 \pm 0.085	0.105 \pm 0.112	0.137	NS
Vertical CDR	0.066 \pm 0.078	0.069 \pm 0.094	0.803	NS
Horizontal CDR	0.064 \pm 0.065	0.064 \pm 0.066	0.942	NS
CDR area	0.032 \pm 0.030	0.039 \pm 0.039	0.093	NS
NRR area	0.136 \pm 0.119	0.197 \pm 0.221	0.009	NS
Inferior NRR	0.069 \pm 0.071	0.078 \pm 0.086	0.349	NS
Superior NRR	0.075 \pm 0.082	0.071 \pm 0.083	0.702	NS
Nasal NRR	0.065 \pm 0.059	0.088 \pm 0.071	0.004	NS
Temporal NRR	0.079 \pm 0.085	0.079 \pm 0.085	0.494	NS

*significant at $p < 0.05$ after Holms-Bonferroni correction

Results 4. Inter-ocular differences: Gender

Inter-ocular differences between males and females were investigated, 199 females and 144 male subjects were included in this study. Unpaired t-tests were used to determine any significant differences between the two groups. The results are shown in table 4.5:

Table 4.5: Inter-ocular differences and Gender.

Parameter	Male inter-eye difference Mean \pm SD	Female inter-eye difference mean \pm SD	2 tailed T-test p-value
IOP	1.140 \pm 0.991	0.955 \pm 0.119	0.063
V disc area	0.022 \pm 0.119	0.001 \pm 0.131	0.400
H disc area	0.014 \pm 0.133	0.022 \pm 0.235	0.306
Disc area	0.037 \pm 0.350	0.011 \pm 0.175	0.643
V cup diameter	0.047 \pm 0.177	0.011 \pm 0.177	0.063
H cup diameter	0.015 \pm 0.183	0.000 \pm 0.121	0.813
Cup area	0.028 \pm 0.171	0.001 \pm 0.096	0.082
Vertical CDR	0.012 \pm 0.131	0.0002 \pm 0.086	0.309
Horizontal CDR	0.005 \pm 0.099	0.002 \pm 0.044	0.617
CDR area	0.010 \pm 0.061	0.022 \pm 0.219	0.028
NRR area	0.009 \pm 0.322	0.006 \pm 0.123	0.661
Inferior NRR	0.025 \pm 0.092	0.016 \pm 0.119	0.012
Superior NRR	0.005 \pm 0.097	0.017 \pm 0.092	0.582
Nasal NRR	0.016 \pm 0.120	0.017 \pm 0.091	0.917
Temporal NRR	0.020 \pm 0.110	0.014 \pm 0.117	0.642

The results show that there is no differences between males and females in either IOP or ONH asymmetry in any of the parameters measured ($p > 0.05$).

Inter-ocular disc asymmetry and IOP asymmetry: Correlations.

No statistically significant correlations were found between ONH asymmetry and the IOP asymmetry in either age group (all $p > 0.05$).

Subjects with a family history of glaucoma

31 subjects reported an immediate family member with glaucoma: sister (3), son (1), father (10), mother (17), brother (2), 4 patients had more than one family member with glaucoma. The inter-ocular differences of these patients were analysed and no statistically significant differences were found compared to the group with no family history (all $p > 0.05$).

Discussion

Main findings

Overall, the right eyes showed thinner nasal NRRs compared with left eyes; however, there was no lateral difference in NRR area. The right eyes also showed thicker temporal NRRs but this just failed to reach significance. The results indicate a displacement of the cup between right and left eyes. The vertical cup diameter was greater in left eyes, no other ocular differences were found between right and left eyes.

The two eyes of an individual were highly correlated for all ocular parameters and IOP. The IOP varied on average by less than 1mmHg, the upper limit of asymmetry was 3mmHg (mean+2SD). The cup area varied on average by 0.1mm, the upper limit of cup area asymmetry was 0.3mm (mean+2SD). The vertical and horizontal cup diameters showed similar inter-eye asymmetry. The NRR thickness also showed similar amounts of inter-ocular variation for all 4 quadrants. The CDR area showed the least inter-ocular variation of all the ONH parameters, with 99.7% of subjects having a CDR area ratio of ≤ 0.2 .

The older age group (≥ 40 years) showed statistically less IOP asymmetry compared with the younger age group; none of the ONH variables showed any differences in asymmetry between the two age groups.

Subjects with a positive family history of glaucoma did not show an increase in inter-ocular asymmetry compared to the control group.

There were no gender differences in either IOP asymmetry or ONH asymmetry.

Laterality: Right Eyes compared with Left eyes.

This study found that the vertical cup diameter was larger in left eyes $p < 0.05$. The vertical disc diameter was also larger in left eyes but this just failed to reach significance ($p = 0.016$); indicating that cup asymmetry increased with disc asymmetry, this was also reported in the Blue Mountains study (Ong et al 1999). The present study also found right eyes showed thinner nasal NRRs compared with left eyes. Overall there was no difference in NRR area between right and left eyes. This indicates a displacement of the cup, possibly caused by a difference in central retinal vessel insertion in the two eyes. This finding has not been previously reported. A study in 2000 by Gherghel et al, found a thicker nerve fibre layer (NFL) in left eyes, particularly in the nasal sector, although the present study measured NRR thickness rather than NFL thickness, the presence of a thicker nasal rim in left eyes was also found. Other studies however have found either no difference in NFL thickness (Mwanza 2010) or right eyes showing thicker NFLs (Herman

2004). The present study did not find any difference in IOP or any of the other ocular parameters between right and left eyes. Few studies have investigated laterality, Durukan (2004) Herman (2004), Vernon (2005) and Gherghel (2000) all found no intraocular differences in the ONH. A small study of 50 children in 2011 found larger CDR area in right eyes (Larsson et al 2011) this was not confirmed in the present study.

Inter-ocular differences

The right and left eyes within individuals were highly correlated for all ocular parameters and IOP. The IOP varied on average by less than 1mmHg, the upper limit of asymmetry was 3mmHg (mean+2SD) and the cup area by 0.1mm², the upper limit of cup area asymmetry was 0.3mm (mean=2SD). The vertical and horizontal cup diameters varied by a similar amount within individuals (0.123mm and 0.122mm respectively). The cup area asymmetry was 0.2mm², this figure agrees with the widely cited paper by Jonas et al (1988). The NRR thickness also showed similar amounts of inter-ocular variation for all 4 quadrants. The CDR area showed the least inter-ocular variation of all the ONH parameters (0.037), this is in agreement with Huynh et al, 2007 who also found the CDR to be the most symmetric parameter in normal eyes. The vertical CDR varied slightly more than the horizontal CDR but this was not clinically significant (0.068 vs. 0.064). In the current study, 99.7% of subjects had a CDR ratio of ≤ 0.2 , this is higher than reported in other studies; however as previously described, the CDR area shows less asymmetry than the vertical or horizontal CDR reported in other studies; Huynh et al (2007) found 94% of subjects had a CDR of ≤ 0.2 , Jonas et al (1988) found the figure to be 96% and in the Blue Mountains study, Ong et al (1999) also found 94% of subjects to have a CDR of ≥ 0.2 . A CDR of 0.2 is commonly used as the cut-off for normality when screening for glaucoma, but as described by Ong et al (1999) using this figure achieves good specificity but only achieves 24% sensitivity in glaucoma detection, reflecting that fact the although more common in Glaucoma, disc asymmetry is still uncommon and cannot be used for screening in isolation. The present study is in agreement with a CDR inter-ocular difference of 0.2 being the upper cut-off for normality.

Inter-ocular differences: Results by age group

The results indicate that IOP asymmetry between eyes does not increase with age. However there does appear to be a small increase in NRR area and nasal NRR thickness asymmetry with age, this could reflect a change in the glial support tissue and loss of retinal nerve fibres with age. The disc area was not statistically significantly different between the two age groups, indicating this remains constant throughout life. The increased NRR variation between fellow eyes in the older age group is unlikely to be caused by poorer image quality, as all of the other inter-ocular parameters showed no

significance. Herman et al (2004), found no differences in inter-ocular differences with age, however subjects with a CDR >0.3 were excluded from that study. The findings of the present study show the differences between the two groups to be small and not likely to be of clinical significance in glaucoma screening. It can therefore be concluded that for glaucoma screening, larger inter-ocular differences are not found in the older age group and that the cut-off for CDR normality at 0.2 is valid for both age groups.

Inter-ocular differences: Results by ethnic group

The data was analysed for ethnic inter-ocular differences. Both groups show a similar degree of IOP asymmetry between fellow eyes. The only ocular parameter to show significance between the two groups was the horizontal disc diameter ($p=0.005$), However after Holms-Bonferrioni correction, this was no longer significant at $p<0.05$. The WE group also showed a greater standard deviation for intraocular differences than the SA group for disc area and NRR area, showing a greater spread of disc sizes for this group. These results show that although the differences are small, the WE group do exhibit larger amounts of inter-ocular variation for some variables than the SA group. It is also worth note that the CDR does not show any difference in inter-ocular variation between fellow eyes between the two ethnic groups. This has not previously been reported and is useful in glaucoma screening when the CDR rule of 0.2 can equally be applied to both ethnic groups.

Inter-ocular disc versus IOP comparisons.

It is well documented that in glaucoma, the eye showing the greater damage is usually the eye with the higher IOP. In normal tension glaucoma where both eyes are within normal limits, it has been shown that the eye with higher IOP shows larger degrees of damage (Cartman 1988). The present study sought to determine any correlation between IOP and ONH inter-ocular asymmetry. No statistically significant correlations were found between any of the ocular parameters and IOP with regards to inter-ocular differences between fellow eyes. It can therefore be concluded that ONH asymmetry cannot be explained by a difference in IOP between eyes in the normal population. This suggests that an eye with a CDR 0.2 larger than the fellow eye and a higher pressure of greater than 3mmHg (Mean+2SD) should alert the clinician that this is outside the normal range as both are independently outside the normal range.

Clinical Relevance

The aim of this part of the study aimed to build up a profile of the normal asymmetry between eyes of an individual. Both ethnic groups and age groups and subjects with/without a family history of glaucoma can be treated the same and a CDR of <0.2 is a reasonable cut-off for normality when assessing patients with less than 2.00D of anisometropia. Although there are small differences in the disc, cup and NRR rims between fellow eyes, the CDR remains remarkably constant and appears to be a good measure of determining abnormal asymmetry, such as that found in glaucoma. It must also be noted that not all glaucoma patients exhibit disc asymmetry and a $CDR > 0.2$, so it is only one factor to consider when screening the population for glaucoma. However if a patient demonstrates a CDR greater than 0.2 they will certainly require further investigation. The upper cut off for IOP asymmetry was 3mmHg for both ethnic groups and age groups. The finding of right eyes showing thicker temporal rims and thinner nasal NRRs than left eyes, although small, may be of clinical relevance, it shows that when assessing a disc for the ISNT rule, the laterality is important.

Appendix 7: The influence of age, gender, IOP, blood pressure, refraction and family history of glaucoma on the optic nerve head topography.

Abstract

Purpose: This study aimed to investigate any possible relationships between optic disc topography parameters as assessed by fundus photography and general variables such as age, gender, IOP, blood pressure and positive family history of glaucoma.

Methods: This cross sectional study was carried out in North West England between February 2010 and February 2011. 348 patients were randomly recruited to the study. All patients underwent general history taking, retinal photography, refraction, intra-ocular pressure and blood pressure measurements. Optic nerve morphology was assessed using computer aided analysis. Multiple regression analysis was used to determine any significant correlations.

Results: Increasing myopia was not associated with increasing disc size or cupping for refractions of $\leq \pm 6.00D$. Hyperopic eyes tended to show increased vertical disc diameter ($p=0.0004$), increased NRR area ($p=0.0002$) and disc area ($p=0.005$) compared with myopic eyes; however this is likely caused by the shorter axial length of hyperopes. Myopia was associated with increased PPA in the nasal sector ($p=0.0034$). Gender differences were found only in the White European group. Females were found to have more vertically oval discs ($p=0.008$) with thicker inferior NRRs ($p=0.017$) compared with males. Males were also found to have a greater vertical CDR ($p=0.003$) than females and a larger horizontal cup diameter ($p=0.008$). No differences in ONH size were found between males and females ($p>0.05$). No significant relationships were found between the ONH appearance and age, IOP, OPP, BP, diabetes, migraine or a positive family history of glaucoma ($p>0.05$).

Conclusion: Refraction $\pm 6.00D$ is not associated with disc size or the degree of cupping. Hyperopic discs tend to be more vertically oval, with a shift to rounder, more horizontal discs towards myopia. Glaucoma screening at a clinical level should assess the ONH independently of IOP, BP, refraction $\pm 6.00D$, vascular status and age.

Introduction

Screening for glaucoma in the community is aimed at patients over 40 years of age due to the known increased risk of glaucoma in this age group, in particular those with a family history of glaucoma. Other potential risk factors for the development of glaucomatous optic neuropathy are less clear due to the interaction of many potential factors including both ocular and non-ocular. There are many factors such as gender, IOP, refraction and vascular status that could potentially affect the ONH appearance; previous studies have investigated these variables but not in the same study.

The relationship between the ONH and refraction has been hotly disputed in the past due to a lack of agreement in the literature. Before the advent of newer imaging devices such as the OCT and HRT, assessment of the disc relied on photographs which were subject to magnification errors; and indirect ophthalmoscopy using a slit lamp, first described by Ruben (Ruben 1994). Slit lamp measurement uses the vertical slit beam height to estimate the vertical disc diameter; however this tends to underestimate the vertical disc diameter (Barr 1999) and can only be used as an approximation. Studies using planimetry tended to find an increase in disc size and cupping with increasing myopia (Tomlinson 1969, Ramrattan et al 1999). These appear to fit the direct ophthalmoscopic appearance of larger discs in myopia, when in fact this is due to ocular magnification. Subsequent studies using newer technology have found no difference with the ONH appearance with low refractions ($\pm 5.00D$) An increase in disc size with myopic eyes over this level (Sing et al 2000) is likely caused by the positive relationship between axial length and disc size (Rudnicka et al 2001, Huynh et al 2006). In the current study, refraction will be investigated independently of age, gender, IOP, OPP, ethnicity or other ONH variables in a multiple regression model

The vascular status of the patient is known to be an important consideration in glaucoma; however its role in the appearance of the normal ONH is less clear. In healthy eyes, blood flow to the ONH remains constant despite BP and IOP fluctuations due to the process of auto-regulation. Increases in IOP have been shown to cause lamina cribrosa displacement and scleral canal enlargement (Sigal et al 2012). Auto-regulation is the process by which in the normal eye the blood flow remains constant despite fluctuations in BP and OPP. However, the ONH itself is a mechanically weak spot and required to tolerate variations in tissue geometry (Sigal et al 2012). In glaucoma patients, auto-regulation either breaks down or its capacity is exceeded by extremes of BP or IOP causing fluctuations in OPP and blood flow (BF). Most studies show a reduction in OPP and blood flow in POAG and normal tension glaucoma (NTG) (Venkataraman et al 2010). Jia et al (2012) also found significantly reduced ONH perfusion in pre-perimetric glaucoma

patients. ONH BF has also been shown to correlate with visual field loss and ONH damage (Resch et al 2011). Hypertension can affect the ocular blood flow (OBF) in two ways: by causing vasoconstriction in order to maintain a constant BF (myogenic autoregulation) and by damaging the microvasculature of the ONH. Hypertension has also been found to raise IOP by increased aqueous production (Costa et al 2009). Myogenic autoregulation is thought to be faulty in patients with glaucoma. Hypotension, vasospasm and migraine have also been implicated as a risk factor for glaucoma, as both a drop in BP or increase in IOP will reduce the OPP if auto-regulation is impaired (Mackenzie et al 2008). The maintenance of the OPP is also thought to be influenced by mechanical properties such as the sclera and lamina cribrosa (Sigal et al 2005). Age has also been shown to cause ONH circulation changes (Shiba et al 2012).

Authors disagree regarding the role of BP in glaucoma, most studies have implicated hypotension in the pathogenesis of glaucoma, especially when secondary to anti-hypertension drugs (Costa 2009). Jonas et al (2006), found increased cupping and thinner NRRs in normal patients with hypotension, most studies since also agree that hypotension results in increased cupping, reduced OPP, reduced NRR area and a greater CDR. Blood pressure dips are also associated with glaucoma progression (Costa 2009). Patients with higher BP are less susceptible to IOP spikes as the OPP and therefore the blood flow is less affected (Liang et al 2009). The inter-relationship between BP and ONH damage is therefore not a simple one.

Study aims

Previous studies have investigated several of the possible variables that may affect the ONH appearance but not in the same study using a multiple regression model. This study aims to determine any relationships between several variables and the ONH appearance. Variables to be investigated include: refraction, blood pressure, age, gender, the presence of a family history of glaucoma, IOP and OPP. Self reported systemic disease including diabetes, hypertension, migraines and headaches which may all affect the vascular supply to the ONH will also be investigated.

Subjects and Methods

Recruitment of participants

Participants free from optic nerve disease were recruited to this study as they attended for an optometric eye examination in a high street practice. Exclusions are given in section 2.1.1.

Ethics approval

Ethical approval was obtained from the Aston University ethics committee prior to the start of this study. The study was designed and conducted according to the principles of the Declaration of Helsinki.

Methods

Details of the investigations and methods are given in Chapter 2. Intraocular pressures were measured using the same non-contact tonometer for all patients. Optic disc analysis was carried out using retinal photography and Navis-lite software. The average value of 3 measurements was recorded for disc and cup size and NRR thickness. Cup depth was estimated by visual inspection of the images and graded 1-4. Eyes were excluded with an IOP over 21mmHg and refraction over $\pm 6.00D$ (BVS).

Statistical Analysis

Pearson's correlation tests were used to identify any possible relationships and these were investigated in a forward stepwise multiple regression analysis using SPSS (version 20). P-values of less than 0.05 were considered statistically significant. One eye from each subject was randomly selected to be included in the analysis by using alternate right and left eyes through the data set (n=360). Parameters included in the multiple regressions were as follows: age, refraction, IOP, gender, refraction, family history of glaucoma, presence of migraines/headaches and diabetes. Ethnicity was also included in the multiple regression analysis

Results

The following variables showed varying degrees of correlation with the ONH variables: systolic blood pressure, gender, age and ethnicity (simple correlation model). These variables were investigated in a forward stepwise multiple regression model.

Results: Ocular Parameters

IOP and Ocular perfusion Pressure

The IOP ranged from 10mmHg to 21mmHg (mean 15.07, SD 2.64) and the OPP ranged from 26-71 (mean 46.17 SD 8.198). Both IOP and OPP were normally distributed due to the upper IOP cut-off of 21mmHg used in this study. The true distribution of IOP is known to be skewed to higher IOP due to normal subjects with ocular hyper-tension, these subjects were excluded from this study. No statistically significant correlations were found between any of the ONH variables and either IOP and OPP at $p < 0.05$.

Refraction

Subjects were excluded if the best vision sphere (BVS) refraction exceeded $\pm 6.00D$. The mean refraction of the sample was 0.06 (range +5.00 to -5.00, SD 1.820). Refraction showed statistically significant simple correlations with disc and NRR variables, no correlations were found between refraction and CDR or cup size. Simple correlations found an increase in superior and nasal NRR width with decreasing myopia, however using stepwise multiple regressions, only the nasal NRR remained significant ($p=0.016$). The NRR area and disc size remained statistically correlated with refraction ($p=0.0002$, $p=0.005$). The results show an increase in NRR width and disc size with a refraction shift away from myopia albeit small, this is illustrated in figures 5.1 and 5.2. (r^2 shows that 4% of the variability in disc size is due to refraction). It can be seen from table 5.1 that as the disc size increased with a hyperopic shift in refraction; this was due to the vertical disc diameter increasing rather than the horizontal. The results show that a prescription shift to increasing myopia is not associated with increased disc size, CDR or cupping for prescriptions $\pm 6.00D$. There was a statistically significant increase in nasal PPA towards myopia ($p=0.003$).

Table 5.1: Refraction and significant ONH correlations

ONH Variable	Pearson's "r"(simple correlations)	Pearson's p-value	β weights* (multiple regression)	p-value	p2-value**
Inferior NRR	0.154	0.03	0.090	0.096	NS
Superior NRR	0.154	0.004	0.131	0.015	NS
Nasal NRR	0.214	<0.0001	0.172	0.001	0.016**
NRR Area	0.263	<0.0001	0.241	<0.0001	0.0002**
Disc Area	0.195	0.0003	0.194	0.0003	0.005**
Horizontal Disc Diameter	0.165	0.002	0.126	0.023	NS
Vertical Disc Diameter	0.203	0.0001	0.231	<0.0001	0.0004**
Nasal PPA	-0.178	0.001	-0.204	0.0002	0.0034**

*multiple regression, standardised β weights shown. ** after Bonferroni's correction (20 disc parameters analysed)

Figure 5.1: NRR area versus refraction (best vision sphere), n=348

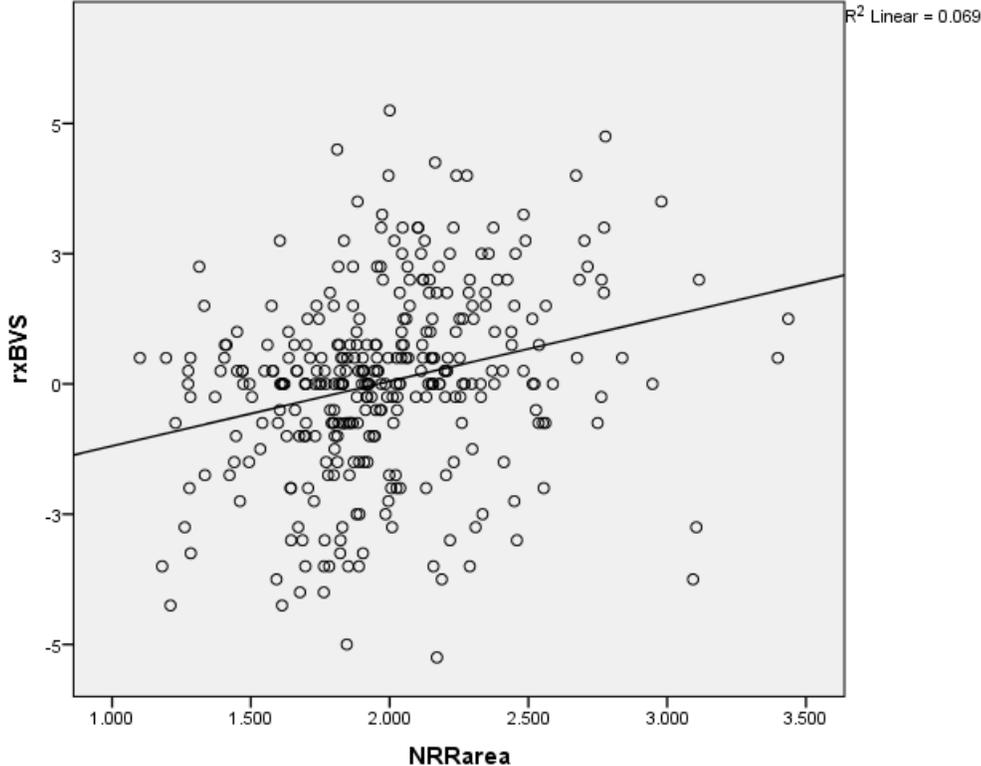
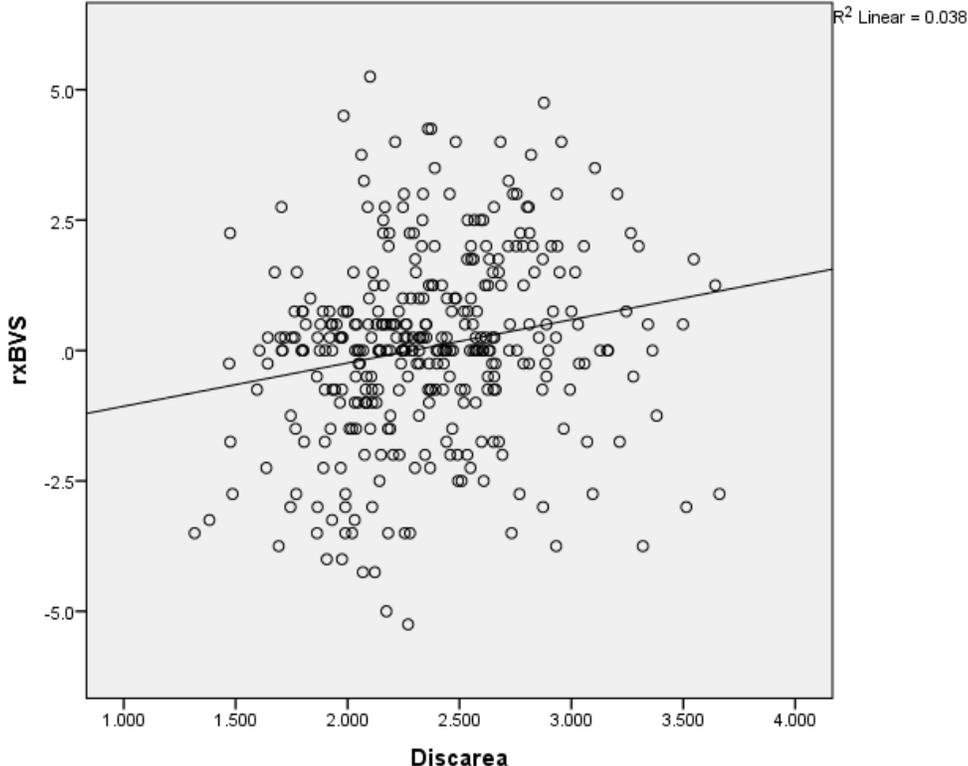


Figure 5.2: Disc Area versus Refraction (best vision sphere) n=348



Results: Systemic Parameters

Blood Pressure

Diastolic BP ranged from 49 to 108 (mean: 74.31, SD: 10.666). Systolic BP ranged from 83 to 187 (mean: 126.74 SD: 18.202). The only significant correlation was between increased systolic blood pressure and superior PPA thickness (“r”=0.167, p=0.002). This was confirmed after stepwise multiple regression (β =0.167, p=0.002) No other correlations were found between both diastolic or systemic blood pressure and ONH parameters.

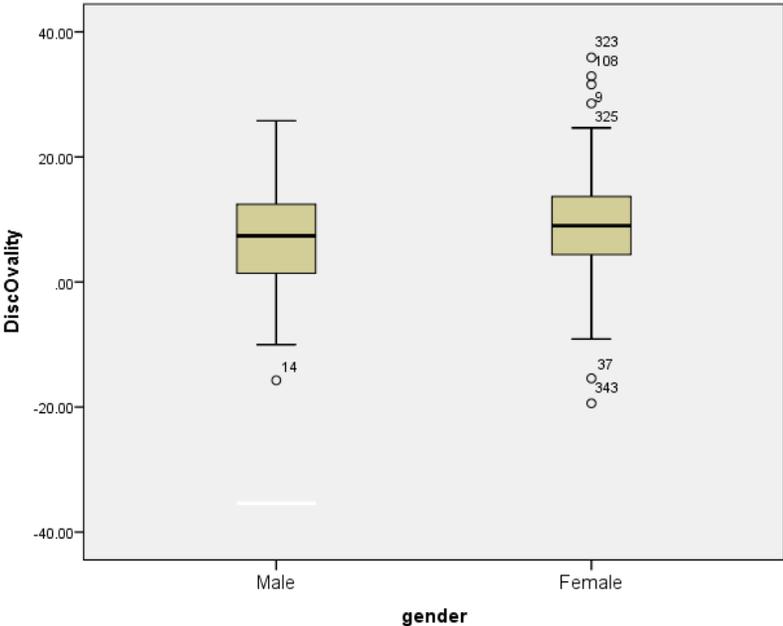
Personal history of vascular disease: Diabetes/Hypertension/migraine

Of the 348 subjects, the numbers with vascular disease were as follows: headaches/migraine: 21, diabetes: 17, hypertension: 87, both hypertension and diabetes: 18. Simple correlations were carried out on the ONH parameters and the self-reported vascular status by the patient. The variables analysed were: diabetes, hypertension, diabetes and hypertension combined, headaches and migraine. The Pearson’s “r” statistic was calculated and none of the vascular disorders described above showed any correlation with any of the ONH parameters (p>0.05).

Gender

145 males and 203 females were included in this study. Simple correlation found several ONH variables to correlate with gender. Forward stepwise multiple regression was performed and Holms-Bonferroni correction applied.

Figure 5.3: Disc ovality and gender



Female gender was significantly and independently correlated with increased disc ovality ($\beta=168$, $p=0.023$) and increased NRR thickness ($\beta=0.169$, $p=0.024$). Female gender was significantly correlated with a decreased vertical CDR ($\beta=-0.181$, $p=0.012$) and decreased horizontal cup diameter ($\beta=-0.174$, $p=0.017$)

Figure 5.4: NRR area and gender

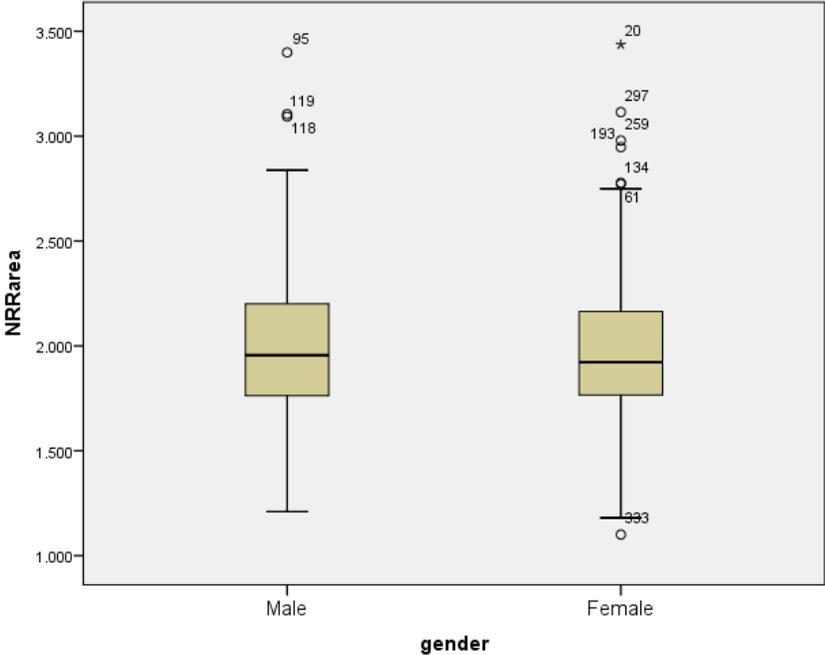


Figure 5.5: Gender versus vertical CDR

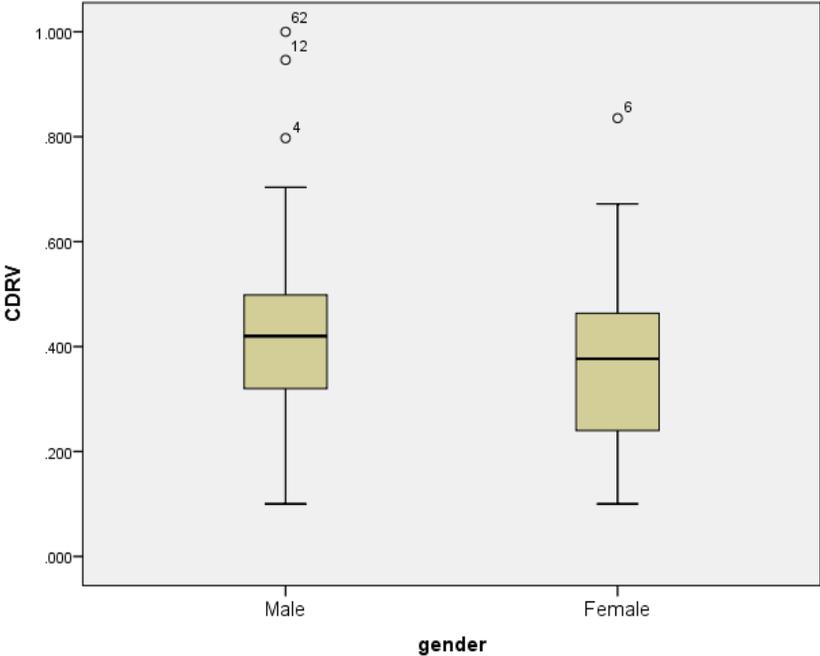
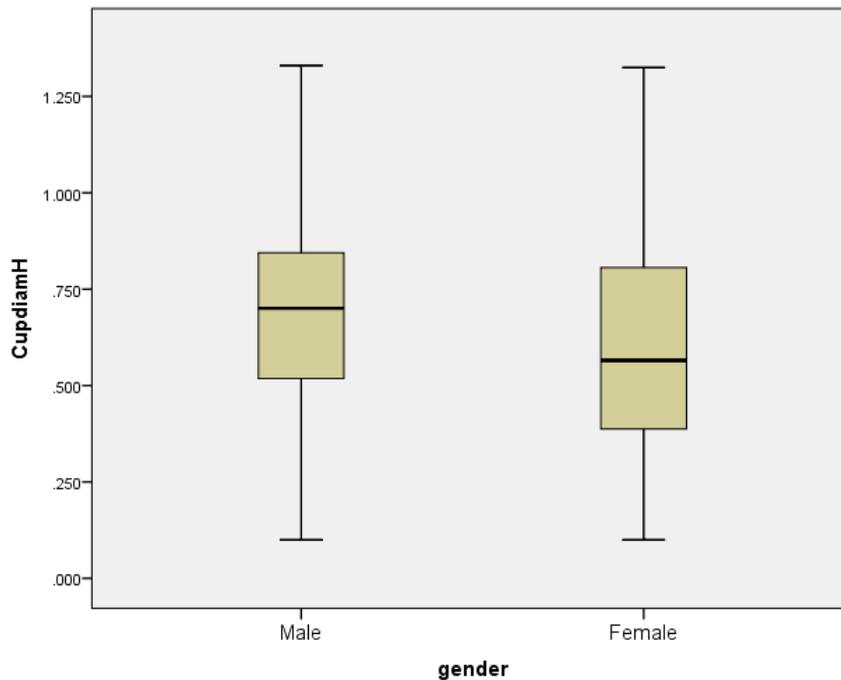


Figure 5.6: Gender versus horizontal cup diameter



The effect of gender on the ONH was analysed for each ethnic group using forward stepwise multiple regression. Only the WE group (n=257) showed gender to have a statistically significant effect on the ONH parameters. Males showed larger horizontal cup diameters ($\beta = -0.216$, $p=0.008$) and larger vertical CDRs ($\beta = -0.231$, $p=0.003$). Females showed greater disc ovality ($\beta = 0.213$, $p=0.008$) and thicker inferior NRRs ($\beta = 0.209$, $p=0.017$). No effect of gender was found in the SA group (n=91).

Age

The age range of the subjects was 16–86 (mean: 48.99 SD: 16.336). Pearson's correlation found significance with age and: nasal NRR ($r=0.183$, $p=0.001$), NRR area ($r=0.183$, $p=0.001$), disc ovality ($r=-0.160$, $p=0.003$), Disc area ($r=0.146$, $p=0.07$) and horizontal disc diameter ($r=0.182$, $p=0.001$).

Forward stepwise multiple regressions were carried out on the data, no significant relationships remained between age and any of the ONH parameters after Bonferroni's correction.

Family history of glaucoma

31 of the 348 subjects reported a family history of glaucoma (8.9%). The family members with glaucoma are shown in table 5.2.

Table 5.2: Reported family history of glaucoma.

Family member	Count (n=31)
Sister	3
Son	1
Brother	2
Mother	17
Father	10

Four patients reported more than one family member with glaucoma. Patients were therefore far more likely to report a parent with glaucoma than a sibling. No correlations were found between the presence of a family history of glaucoma and the ONH variables.

Discussion

Main findings

There was no clinically significant relationship between refraction and ONH cupping. No increase in ONH size or cupping was found with increasing myopia ($\pm 6.00D$). A refraction shift towards hyperopia was positively correlated with increased vertical disc diameter ($p < 0.05$).

Blood pressure, vascular status, age and the presence of a family history of glaucoma did not show any significant relationship with ONH variables in this study.

Females show a more vertically oval disc shape compared with males and a smaller horizontal cup diameter in the WE group only ($p < 0.05$), there was no difference in disc size between males and females.

IOP and OPP

For the included subjects within the normal IOP range ($\leq 21\text{mmHg}$), there were no relationships between IOP and any ONH parameters, this is in agreement with most studies (Burgoyne et al 2008) but in disagreement with a study by Abe (2009) who found an increase in cupping with IOP. Most studies have investigated ocular hypertensive patients rather than normals. It is likely that ocular hypertensives with an IOP over 21mmHg would show ONH changes but these patients could be regarded as in the early stages of glaucoma and so were excluded from this study. Due to the complex

relationship between IOP and BP and their effect of ocular blood flow, it is perhaps not surprising that IOP does not directly impact on the ONH appearance within the normal IOP range.

Refraction

The results show that there is an increase in ONH size and NRR thickness towards hyperopia; this was also found by Abe et al (2009) and is opposite to that usually reported in the literature which normally suggests either no ONH changes or a small increase with myopia. Most studies have found no significant change in the ONH with refraction (Tong et al 2007, Rudnicka et al 2001, Sing et al 2000, Durukan et al 2004), however some authors have found myopia is associated with an increase in ONH area (Ramrattan et al 1999, Tomlinson 1969). The conflicting results regarding refraction and ONH parameters is likely due to difficulties in imaging the in-vivo ONH, with differences in correction factors and methods of imaging, particularly in the earlier studies.

Fundus cameras often use telecentric optics (as in the current study) in which the anterior focal point of the first lens is made coincident with the first principal point of the eye, this is done by estimating the reduced distance from the second principal point of the eye to the fovea by the use of refraction, refraction and corneal curvature or axial length and corneal curvature (Meyer et al 2001). The actual methods employed by manufacturers vary, and so results cannot be directly compared between studies and require normalisation factors. In the current study, the telecentric correction for refraction was confirmed in the methods section using contact lenses to change the eyes refraction.

The results suggest that axial length was playing a part in the results, as both NRR and disc size were the largest ONH variables measured and are more likely to be affected by axial length; myopes tend to have longer axial lengths which may result in smaller images. Rudnicka et al (2001) found that increasing axial length had more positive associations with ONH parameters than refraction. Axial length does not however account for a statistically significant relationship between the vertical disc diameter and refraction but not the horizontal disc diameter which may reflect real differences between refractive groups; hyperopic eyes having a more vertically oval disc shape than myopic eyes. An increase in myopia was associated with an increase in the amount of nasal PPA, this was statistically significant. Further research is needed however, to remove axial length as a confounding factor.

Blood Pressure

This study found no relationship between hypertension, migraine or diabetes and ONH variables. However, due to the self-reported nature of these conditions and lack of

medical records available, the information gathered is likely to be incomplete. Patients very often were unsure what conditions they had or what medications they were taking or what for. Often the duration or severity of the condition was unknown. Further study into this area is warranted with access to the patient's medical records. The weight of evidence from other studies suggests a greater CDR and thinner NRR with hypotension, although this may not be applicable to the normal population. The present study suggests however, that these conditions do not impact on the ONH appearance at a clinical level.

Vascular disease: diabetes/hypertension/migraine

Diabetes causes damage to the microvasculature of the eye, including the ONH, this may cause increased susceptibility to glaucomatous damage due to changes in auto-regulation and consequently ocular blood flow to the ONH. Similarly, migraine is associated with dips in blood pressure which are known to reduce ocular blood flow to the optic nerve head and are implicated in the pathogenesis of normal tension glaucoma. However, in the present study, the self reporting nature of the information proved problematic. No information was available on the severity or control of the diabetes or the severity of migraine which was open to patient interpretation. The populations in these subgroups were also small and so although no associations were found in the present study, this area warrants further study.

Gender

This study did not find any significant difference in the ONH size between males and females; this is in agreement with several studies: Jonas et al 1988, Huynh et al 2006, Hermann et al 2004. Several studies however have found the ONH to be smaller in females (Akar et al 2004, Bourne et al 2008, Kashiwagi et al 2000, Vernon et al, Rudnicka et al 2001, Ramrattan et al 1999), although many of these studies show borderline significance (Sing et al 2000). Differences were found however in the ONH shape and several ONH parameters.

Age

Age did not show any relationship with any of the ONH variables. An increase in cupping might be expected with age due to the known loss of ganglion cells with age (Balazsi et al 1984). There is a corresponding loss of RNFL with age which is most pronounced in the superior quadrant and slowest in the inferior quadrant (Feuer et al 2011, Parikh et al 2007, Da Pozzo et al 2006), however this does not translate to the clinical ONH appearance, perhaps due to an increase in glial support cells. Despite the loss of RNFL with age, most studies have not found a loss of NRR with age (Funk et al 1989, Kashiwagi et al 2000, Jonas et al 2003, Ramrattan et al 1999, Quigley et al 1990, Varma et al 1994, Britton et al

1987). However, Knight et al in 2012 found a decrease in rim thickness with age using Cirrus HD-OCT; However, Hsu et al (2012) found no relationship with age and RNFL thickness, also using the OCT. Some studies however, have found an increase in the CDR with age (Kergoat et al 2001, Bengtsson et al (1976), Abe et al 2009), many of these studies also found an increase in disc area with age, it is not clear why this should be as the posterior scleral canal does not change from childhood (Jonas 2003). The disagreement in the literature supports the current study's findings that there are no clinically significant changes in the ONH appearance with age.

Positive family history of glaucoma

The presence of a positive family history of glaucoma was not associated with any ONH parameters. This study suggests that family members of a glaucoma sufferer do not show genetic differences from the rest of the normal population. However several genetic markers in glaucoma sufferers have been identified (Gasten 2012), but it appears that they are not clinically expressed in family members. Due to the small sample sizes, further study in this area is warranted.

Clinical Relevance

The ONH should be assessed independently of age, refraction ($\pm 6.00D$), IOP, vascular status and a positive family history of glaucoma at a clinical level.

Study Limitations

The effect of blood pressure was assessed from the measurements taken on the day of the visit by using an average of 3 readings. White coat syndrome is well documented and although likely to be less in an optometric practice than general practice, is still a factor, some patients were more nervous than others when examined. Patients on medication for hypertension were likely to have normal readings when measured. Many vascular variables may affect the ONH appearance such as the duration of untreated BP, severity of BP, confounding disease etc. Although no relationships were found between vascular disease, BP and ONH appearance in this study; this cannot be ruled out and warrants further study.

The influence of vascular disease was limited by the self-reporting nature of these conditions; the medical history of each patient was not available resulting in the accuracy of this information being unreliable in many cases. This was particularly evident in migraine and headache which was down to personal interpretation. However, in glaucoma screening, this accurately reflects the nature of the information provided by the patient to the optometrist and is not clinically relevant when assessing the ONH in practice.

The effect of refraction on the ONH appearance was limited by the absence of axial length measurements, resulting in images from hyperopic eyes suffering from a degree of magnification compared to myopic eyes. This did however not affect the CDR results. Future studies on refraction should include axial length measurements.

Appendix 8: The influence of the disc size and shape on other optic disc topographic parameters in the normal population.

Abstract

Purpose: This study aimed to investigate the influence of disc size and shape on cupping and NRR thickness in the normal population.

Methods: This cross sectional study was carried out in North West England between February 2010 and February 2011. 348 patients were randomly recruited to the study. All patients underwent retinal photography, refraction, intra-ocular pressure and blood pressure measurements. Optic nerve morphology was assessed using computer aided analysis.

Results: As disc area increased, the cup area, CDR and NRR area also increased ($p < 0.0001$) and the discs became rounder and less vertically oval in shape ($p = 0.001$). As the vertical disc diameter increased, the inferior NRR became thicker ($p = 0.001$). As the horizontal disc diameter increased, the nasal NRR increased ($p < 0.0001$). Larger discs tended to have rounder and less vertically oval cups and more closely followed disc shape than small discs. With a more vertically oval disc, the cup tended to follow disc shape less closely resulting in a thicker superior and inferior NRR ($p = 0.001$ and $p = 0.003$ respectively).

Conclusion: Smaller discs tend to be more vertically oval, with a shift to rounder, more horizontal discs towards increasing disc size. Small discs will therefore tend to have thicker superior and inferior NRRs relative to the nasal and temporal thickness compared with larger discs. Disc ovality was independent of cup ovality. Disc size and shape therefore need to be considered when assessing the NRR thickness.

6.2 Introduction

Glaucoma screening ideally should include the assessment of the ONH appearance, IOP and visual field (VF) testing but in reality this is unfeasible outside optometric practice. Any wide spread glaucoma screening programme using images relies on the ONH appearance alone. Currently in the UK, diabetic patients undergo yearly retinal photography which are assessed remotely by clinicians, it is possible in the future that these same images could also be used to assess the disc for glaucoma. It is crucial to know the glaucoma detection rate using ONH analysis alone. The European optic disc assessment trial in 2010 found glaucoma detection rates of 80% using stereo photographs (Reus et al 2010). Computerised systems such as the OCT and HRT II tend to outperform clinicians with the exception of glaucoma specialists. (Reus et al 2010, Deleón-Ortega et al 2006). These systems incorporate algorithms such as the Moorfields regression software used in the HRT-II and the Disc Damage Likelihood Scale (DDLs) (Spaeth 2002). The DDLs takes into account the disc size and NRR width and was found by Damesh-Meyer et al (2006) to be more accurate than the HRT-II Moorfields analysis. Computerised glaucoma screening using images therefore has the potential for wide spread screening in the community and it is crucial for the software to have an accurate database of the normal population and the inter-relationship between ONH parameters.

There have been many studies that have investigated the relationship between the size of the disc, cup and NRR width, both in the glaucoma and normal populations. However most studies do not correct for possible confounding factors such as age, refraction, ethnicity, refraction, IOP or OPP. In considering the CDR, it is the vertical CDR that is often reported in the literature (Healey et al 1999), as it is this that tends to increase in glaucoma, there is less mention of the horizontal CDR or CDR area relative the disc. Both the degree of cupping and the NRR width have been shown to be influenced by size of the disc (Sing et al 2000) but it is less clear if disc shape has a role. The concept of the CDR was first proposed by Armaly in 1967 as a way of recording the ONH appearance and helping to identify glaucoma (Armaly 1967, 1969) this was followed by the CD area ratio described by Tomlinson in 1969. The CDR is the most common disc description recorded in optometric records. It is well established in the literature that as disc size increases, so does the cup size and NRR thickness (Nakamura et al 1998, Healey et al 1997, Huynh et al 2006, Crowston et al 2004, Sing et al 2000). The shape of the disc and the influence on cup size and shape has been less well investigated and will be addressed in this current study.

Study aims

This section of the study aims to investigate the inter-relating ONH variables such as the relationship between ONH size, NRR thickness, cupping, disc and cup shape. Any positive correlations will assist in building up a profile of the normal ONH and how the appearance varies in the general population.

Subjects and Methods

Recruitment of participants

Participants free from optic nerve disease were recruited to this study as they attended for an optometric eye examination in a high street practice. Exclusions are given in section 2.1.1.

Ethics approval

Ethical approval was obtained from the Aston University ethics committee prior to the start of this study. The study was designed and conducted according to the principles of the Declaration of Helsinki.

Methods

Details of the investigations and methods are given in Chapter 2. Intraocular pressures were measured using the same non-contact tonometer for all patients. Optic disc analysis was carried out using retinal photography and Navis-lite software. The average value of 3 measurements was recorded for disc and cup size and NRR thickness.

Statistical Analysis

One eye from each subject was randomly selected to be included in the study. Pearson's correlation tests were used to identify any relationships. P-values of less than 0.05 were considered statistically significant.

Results

The present study found slightly lower values than Jonas et al (1999) for disc values and significantly smaller cup diameters, likely due to differing methods of measurement which is a confounding issue when comparing studies. A summary of the measured disc variables for all subjects and WE subjects is given below in table 6.1, together with the widely cited results of Jonas:

Table 6.1: ONH measurements: All ethnic groups and White European (WE) compared with the results from Jonas et al (1988).

ONH Variable	All subjects Mean \pm SD n=348	WE population Mean \pm SD n=257	Jonas 1988* Mean \pm SD (WE population) n=457
ONH area	2.361 \pm 0.426	2.368 \pm 0.178	2.69 \pm 0.70
ONH vertical diameter	1.806 \pm 0.173	1.794 \pm 0.178	1.92 \pm 0.29
ONH horizontal diameter	1.669 \pm 0.802	1.678 \pm 0.189	1.76 \pm 0.31
Cup area	0.383mm ² \pm 0.262	0.356mm ² \pm 0.262	0.72mm ² \pm 0.70
Cup vertical diameter	0.659 \pm 0.310	0.618 \pm 0.319	0.77 \pm 0.55
Cup horizontal diameter	0.606 \pm 0.296	0.574 \pm 0.303	0.83 \pm 0.58
Cup C/D area ratio	0.167 \pm 0.887	0.158 \pm 0.088	
CDR vertical	0.371 \pm 0.161	0.357 \pm 0.169	
CDR Horizontal	0.364 \pm 0.154	0.343 \pm 0.157	

*Jonas et al 1988: Invest Ophthalmol Vis Sci 29:1151-1158

Disc size and shape: influence on cupping

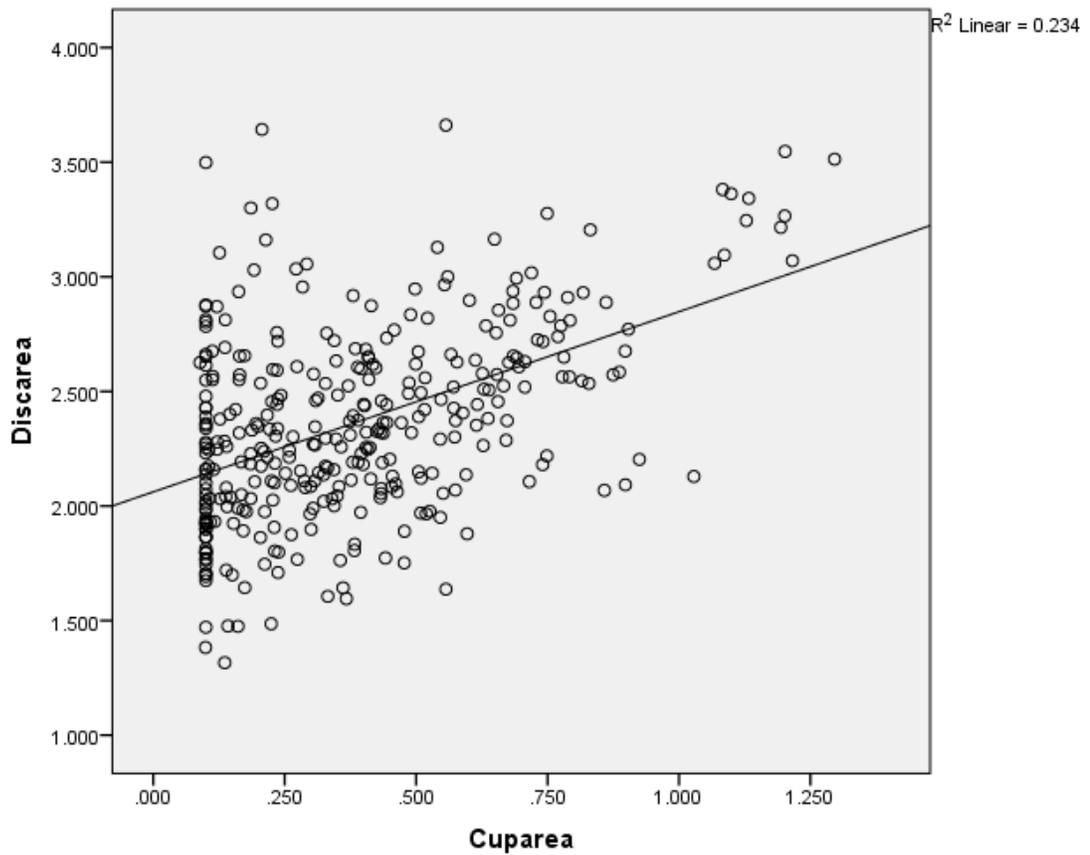
Pearson's correlations found that the vertical disc diameter, horizontal disc diameter and disc area all positively correlated with the cup size (horizontal and vertical cup diameter and cup area) and the CDR (vertical, horizontal and CDR area) at $p < 0.05$. Cupping and CDR therefore increased with disc size. Disc ovality was negatively correlated with disc area ($r = -0.172$, $p = 0.001$); therefore as the disc size increased, the disc became less vertically oval. No correlations were found between disc ovality and cup size or shape, cup ovality was independent of disc ovality ($p > 0.05$).

Table 6.2: Disc size and shape: Influence on cupping

	Vertical Diameter	Disc	Horizontal diameter	disc	Disc Area	Disc Ovality
Vertical cup diameter	r=0.381 p<0.0001*		r=0.357 p<0.0001*		r=0.416 p<0.0001*	r=-0.019 p=0.718
Horizontal cup diameter	r=0.328 p<0.0001*		r=0.392 p<0.0001*		r=0.406 p<0.0001*	r=-0.129 p=0.017
Cup Area	r=0.423 p<0.0001*		r=0.438 p<0.0001*		r=0.484 p<0.0001*	r=-0.077 p=0.150
Cup Ovality	r=0.148 p=0.006*		r=0.06 p=0.266		r=0.124 p=0.021	r=0.077 p=0.153
Vertical CDR	r=0.219 p<0.0001*		r=0.242 p<0.0001*		r=0.252 p<0.0001*	r=-0.061 p=0.259
Horizontal CDR	r=0.220 p<0.0001*		r=0.210 p<0.0001*		r=0.239 p<0.0001*	r=-0.019 p=0.730
CDR Area	r=0.221 p<0.0001*		r=0.238 p<0.0001*		r=0.248 p<0.0001*	r=-0.053 p=0.327

* significant at p<0.05 after Holms-Bonferroni correction

Figure 6.1: Disc area and cup area (n=348)



Disc size and shape: Influence on NRR thickness

Vertical disc ovality showed significant positive correlations with the inferior and superior NRR thickness ($p=0.003$ and $p=0.001$) and a negative correlation with NRR area ($p=0.006$) and nasal NRR thickness ($p<0.0001$) but not with the temporal NRR thickness. The results show that increasingly oval discs exhibit thicker inferior and superior NRRs and thinner nasal NRRs (table 6.3). Disc size is positively correlated with NRR area, but poorly correlated with inferior and superior NRR thickness. Vertical disc diameter was positively correlated with inferior NRR thickness ($p=0.001$) and horizontal disc diameter was positively correlated with NRR thickness ($p<0.0001$).

Table 6.3 Disc size and shape: Influence on NRR thickness (Pearson's r)

	Vertical Disc Diameter	Horizontal disc diameter	Disc Area	Disc Ovality
NRR Area	$r=0.669$ $p<0.0001^*$	$r=0.700$ $p<0.0001^*$	$r=0.789$ $p<0.0001^*$	$r=-0.149$ $p=0.006^*$
Inferior NRR	$r=0.171$ $p=0.001^*$	$r=0.025$ $p=0.648$	$r=0.106$ $p=0.047$	$r=0.157$ $p=0.003^*$
Superior NRR	$r=0.054$ $p=0.320$	$r=-0.086$ $p=0.108$	$r=-0.019$ $p=0.729$	$r=0.171$ $p=0.001^*$
Nasal NRR	$r=0.099$ $p=0.066$	$r=0.263$ $p<0.0001^*$	$r=0.220$ $p<0.0001^*$	$r=-0.219$ $p<0.0001^*$
Temporal NRR	$r=-0.43$ $p=0.423$	$r=0.016$ $p=0.767$	$r=-0.015$ $p=0.774$	$r=-0.074$ $p=0.171$

*Significant correlations at $p<0.05$

PPA: There was no statistically significant relationship between disc size, cupping or NRR thickness and PPA for normal eyes at $p<0.05$.

Discussion

Main findings

Increasing disc size is associated with an increase in cupping, CDR and NRR area. The position of the cup within the disc is variable resulting in poor correlation of disc size with sector NRR thickness. As discs increase in size, they tend to become rounder and less vertically oval in shape.

Cup size increases with disc size but not equally in all quadrants. Discs that are more horizontally oval or rounder in shape will tend to have their cups following the disc shape. Vertically oval discs will have less oval cups compared with the disc shape and therefore show thicker superior and inferior NRRs. Increasing cup size is associated with thinner NRRs, however the NRR area remains unchanged by virtue of the disc becoming larger.

Inter-relating ONH variables

This study aimed to explore the complex relationships between the disc, cup and NRR, corrected for age, gender, refraction, IOP, OPP and ethnicity.

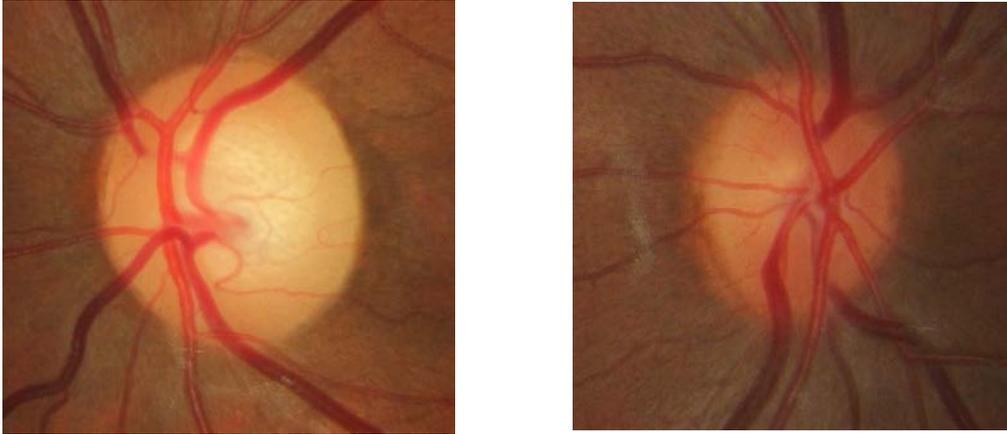
Disc size and shape

The previously reported finding of a vertically elongated disc shape (Jonas et al 1988) was confirmed in the present study. However the horizontal disc diameter showed far more variability than the study by Jonas (SD of 0.802 compared with 0.31 found by Jonas), the variability in the vertical disc diameters were similar (SD 0.173 compared with SD 0.29), this is likely due to the inclusion of the SA population which has been shown in chapters 3 and 5 to be associated with a more vertically oval disc shape. Analysis of the horizontal disc diameter of the WE population found a much lower SD compared with the mixed population (SD 0.189).

Cup size increases with disc size, this agrees with the several studies (Healey et al 1997, Sanfilippo et al 2010, Nakamura et al 1999, Sing et al 2000, Huynh et al 2006) although not equally in all quadrants. As the disc increased vertically, the inferior NRR increased and as the disc increased horizontally in size the nasal NRR increased. As the disc area increased the cup size, CDR and NRR area all increased in size. As discs increased in size they tended to become less vertically oval in shape. This highlights the importance of considering disc size in glaucoma screening. This can be approximated in practice using indirect ophthalmoscopy using a slit lamp, other methods such as comparison with vessel diameter are less ideal as smaller discs tend to have relatively smaller vessels (Lee 2007).

As the disc increased in size both the vertical and horizontal cupping increased. As the horizontal disc diameter increased, so did the horizontal cup diameter, as the disc became more vertically oval, the cup enlarged vertically, in agreement with Healey et al (Blue mountains study 1999). However, the increase in vertical cupping did not keep pace and showed proportionally less increase (table 6.2 shows no correlation between disc and cup ovality).

Figure 6.2: Large Disc vs Small disc: note the disc size relative to vessel diameter

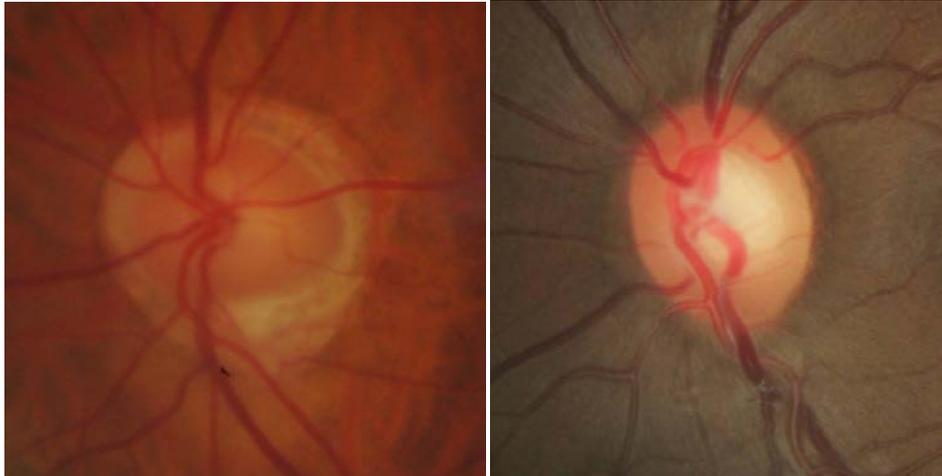


The present study found the cup to be slightly vertically elongated compared with previous studies on WE populations which have found the cup to be horizontally elongated (Jonas et al 1999) or circular (Huynh et al 2006); this is unlikely to be due to the vertical disc ovality of the current population sample, as disc and cup ovality did not correlate ($p>0.05$). The cup size in the present study was smaller than that found by Jonas, this may be due to differing methods of assessing the cup; in the present study, flat discs were assigned a C/D of 0.1 and the image software was unable to handle a CDR of less than 0.2, these discs were also classified as a CDR of 0.1. Other studies may exclude flat discs from their analysis resulting in a mean larger cup size.

The vertical and horizontal cup diameters were both positively correlated with disc size, CDR ratios were negatively correlated with NRR thicknesses in all sectors at $p<0.05$. Larger cups are therefore associated with larger discs and thinner NRR thicknesses but did not correlate with NRR area ($p>0.05$).

As expected, the cup ovality correlated positively with the vertical disc diameter and negatively with the horizontal disc diameter and disc area values but showed no correlation with the CDR values or NRR area. Cup ovality therefore decreases with increasing disc size. Cup ovality was highly correlated with NRR in all 4 quadrants but not with the overall cup area. As the cup ovality increased, the inferior and superior rim also increased, indicating the cup shape did not mirror the disc shape.

Figure 6.3: Study photographs showing differences in disc ovality.



Although the cup size correlated with disc size, the results show that discs that are more vertically oval will have thicker superior and inferior NRRs and thinner nasal NRRs compared with rounder discs. This is a clinically significant finding as an indication of early glaucomatous loss can be a vertical enlargement of the cup and loss of the ISNT rule. Vertical cup ovality has been shown to be greater in glaucomatous eyes (Sanfilippo et al 2010). A vertically enlarged cup in a vertically oval disc may therefore be missed. In contrast, a more horizontally oval or rounder cup will show a thinner NRR in the superior and inferior quadrants and may be cause for a false positive glaucoma referral. In addition, two studies have suggested that glaucomatous eyes have more vertical discs: Sanfilippo et al 2010 and a genetic study by Fan (2011) found that certain genetic traits associated with a larger vertical CDR have a higher risk of glaucoma. Close examination of the disc and cup shape with knowledge of these differences is therefore important in glaucoma screening. This also suggests that application of the ISNT rule may not be appropriate to all disc shapes; this will be investigated in the chapter 7.

Clinical Relevance

The increasing use of ONH imaging systems in glaucoma monitoring and their potential use as glaucoma screening tools makes it essential that the software accounts for differences in the normal population with regard to disc and cup size and shape and NRR thickness between different groups of patients. This study suggests that disc shape in addition to disc size has a large impact on the size and shape of the cup and correspondingly the NRR thickness. The use of disc and cup shape in glaucoma screening has also been proposed by Sanfilippo et al (2010) who suggested that cup shape be used as a discriminator for glaucoma, however, as found in the current study, this needs to be considered with regard to the disc shape. Segmentation analysis of colour

images of the disc has also been suggested as useful in glaucoma screening (Joshi et al 2011), however these systems are limited by automated disc and cup margin recognition. Factors affecting the disc shape including ethnic background, refraction and to a lesser extent gender should also be included in the software. Imaging systems can provide an indication of normality such as the DDL (disc damage likelihood) scale, devised by Spaeth et al (2002), have been shown to have a greater predictive power than assessment of the CDR of clinical examination (Danesh-Meyer et al 2006). The Moorfields regression software is used by the HRT II to grade the disc as normal, abnormal or borderline.

The current study suggests that computer algorithms should also include disc shape in addition to disc size as a variable when detecting glaucoma. It is possible in the future that data mining could be used to include all of the patient and disc variables (size and shape) that impact on the degree of cupping and NRR thickness in order to give a calculation of the likelihood of glaucoma; this could also be combined with IOP and visual field results.