

**EVALUATION OF CENTRAL CORNEAL THICKNESS,
ANTERIOR CHAMBER DEPTH AND AXIAL LENGTH
AMONG JUVENILE OPEN ANGLE GLAUCOMA PATIENTS**

BY

DR AHMAD MARWAN BIN AZIZ @ ABDUL AZIZ

P-UM0123/18

**DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENT FOR THE DEGREE MASTER OF
MEDICINE (OPHTHALMOLOGY)**



SCHOOL OF MEDICAL SCIENCES

UNIVERSITI SAINS MALAYSIA

2022

DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged. I declare that I have no financial interest in the instruments in this study.

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DR AHMAD MARWAN BIN AZIZ @ ABDUL AZIZ
P-UM0123/18
25 October 2022

ACKNOWLEDGEMENT

To begin this acknowledgement, I would like to convey my gratitude and appreciation to my main supervisor, Associate Professor Dr Azhany Yaakub and co-supervisor Professor Liza Sharmini Ahmad Tajudin for their exemplary guidance and unending support throughout this dissertation preparation.

My gratitude also goes to all the lecturers in the Department of Ophthalmology & Visual Sciences, School of Medical Sciences, Universiti Sains Malaysia, technicians, supporting staffs, and all my ophthalmology colleagues and family for their constant support and willingness to help in the process of completing this dissertation. In addition, I would like to express my appreciation to all patients for their involvement and cooperation.

I would also like to extend my gratitude to Dr Siti Azrin Ab Hamid and all lecturers from Biostatistics Unit, School of Medical Sciences, Universiti Sains Malaysia, Dr Norhalwani Husein, Head of Departement, Hospital Raja Perempuan Zainab II, and Dr Farrah Binti Ja'afar, Glaucoma Consultant, Hospital Sultanah Bahiyah.

Last but not least, I would like to extend my heartfelt gratitude to my wife Nur Shahada Binti Jalil, both my daughter and son, Iman Humairah Binti Ahmad Marwan and Ilham Muhaimin Bin Ahmad Marwan for their continuous support and understanding. I would also like to dedicate this effort to my parents for their endless prayers and unwavering faith in me.

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LIST OF ABBREVIATIONS

ACD:	Anterior chamber depth
AGIS:	Advanced Glaucoma Intervention Study
AS-OCT:	Anterior segment-optical coherent tomography
AL:	Axial length
CCT:	Central corneal thickness
CPG:	Clinical practice guideline
HVF:	Humphrey visual field
JOAG:	Juvenile open angle glaucoma
IOP:	Intraocular pressure
IOL:	Intraocular lens
LT:	Lens thickness
MD:	Mean deviation
mm:	Millimetres
OCT:	Optical coherent tomography
PACG:	Primary angle closure glaucoma
POAG:	Primary open angle glaucoma
VA:	Visual acuity
WTW:	White to white
HRPZ II:	Hospital Raja Perempuan Zainab II
HSBAS:	Hospital Sultanah Bahiyah Alor Setar
HUSM:	Hospital Universiti Sains Malaysia

ABSTRAK

PENGENALAN

Glaukoma Sudut Terbuka Juvana (JOAG) adalah subset kepada Glaukoma Sudut Terbuka Primer (POAG), yang bercirikan bentuk pewarisan autosomal dominan. Didiagnosa pada awal umur, pesakit JOAG dijangka akan mempunyai jangka hayat yang lebih panjang. Mereka kebiasaannya akan mengalami kemerosotan penyakit yang lebih cepat. JOAG bermula secara perlahan dan biasanya dikesan pada tahap akhir penyakit apabila kerosakan saraf optik menjadi lebih teruk dan tekanan intraokular melebihi 40mmHg. Pengesanan yang lebih awal biasanya diperolehi dengan adanya saringan pada ahli keluarga pesakit JOAG tersebut. Literatur berkenaan ciri-ciri morfologi JOAG adalah terhad. Dengan mengkaji ciri-ciri tersebut boleh membantu doktor untuk menentukan ciri morfologi yang manakah berkait rapat dengan kemerosotan penyakit. Manakala ahli-ahli keluarga yang didapati mempunyai ciri morfologi yang berkaitan akan disaring dengan lebih kerap, sekaligus menghalang kelewatan pengesanan penyakit.

OBJEKTIF

Kajian ini bertujuan untuk mengkaji ketebalan kornea (CCT), kedalaman kamar anterior (ACD), dan panjang bola mata (AL), pada pesakit JOAG, dan hubungannya dengan tahap keterukan JOAG.

METODOLOGI

Kajian rentas prospektif dijalankan dari Jun 2020 sehingga November 2021 melibatkan 3 pusat oftalmologi tertuari. Kajian melibatkan 2 kumpulan pesakit, iaitu kumpulan JOAG dan

kumpulan kawalan. Tahap JOAG adalah berdasarkan ‘Modified Advanced Glaucoma Intervention Study’ (AGIS) menggunakan analisis medan penglihatan Humphrey SITA program 24-2 yang berkualiti. Imbasan-A (A-scan) telah dilakukan untuk mengukur ACD, dan AL. Manakala imbasan tomografi optik koheren (OCT) telah dibuat untuk mengukur CCT.

KEPUTUSAN

Seramai 120 pesakit telah direkrut. Seramai 60 pesakit JOAG and 60 pesakit kawalan telah diperolehi. Bilangan pesakit lelaki melebihi bilangan pesakit wanita sebanyak 53.5% (n = 32) didalam kumpulan JOAG, dan 51.7% (n = 31) didalam kumpulan kawalan. Umur min adalah 27.97 ± 7.1 tahun dalam kedua-dua kumpulan. Majoriti dari pesakit JOAG, berada pada tahap teruk 68.3% (n = 41), diikuti dengan tahap awal 26.7% (n = 16), dan tahap pertengahan 5% (n = 3), ketika presentasi pertama. Manakala pada waktu kajian dijalankan, majoriti pesakit JOAG adalah dari tahap akhir, meningkat kepada 70% (n = 42), diikuti dengan tahap awal 16.7% (n = 10), dan tahap pertengahan 13.3% (n = 8). Perbandingan kumpulan JOAG dengan kawalan menunjukkan bacaan min yang signifikan secara statistik pada ukuran CCT (556.23 ± 28.93 mm, $p=0.008$) dan AL (25.16 ± 1.63 mm, $p < 0.001$) dari kumpulan JOAG. Ujian regresi multi linear, menunjukkan faktor yang berkaitan dengan tahap keterukan JOAG ialah bacaan IOP awal presentasi dan AL.

KESIMPULAN

Terdapat perbezaan min yang signifikan antara CCT dan AL antara kumpulan JOAG dan kumpulan kawalan. Bacaan IOP presentasi awal dan AL adalah faktor risiko yang berkaitan dengan kemerosotan penyakit JOAG.

ABSTRACT

INTRODUCTION

Juvenile open-angle glaucoma (JOAG) is a subset of primary open-angle glaucoma (POAG), characterized by a pattern of autosomal dominant inheritance. Diagnosed at early age, patients with JOAG are expected to have longer life expectancy. They are usually associated with more severe and rapidly progressive disease. JOAG has insidious onset and is usually detected late stage of the disease with typically advance optic nerve damage and intraocular pressure of more than 40mmHg. Early detection particularly due to screening of family members with positive family history of JOAG. Literature on morphologic features of JOAG is limited. By studying those features will help clinician in determining which morphologic features associated with progression of the disease. While family members with positive morphologic features particularly will be screened more regularly, preventing late detection of the disease.

OBJECTIVE

The study aims to evaluate central cornea thickness (CCT), anterior chamber depth (ACD) and axial length (AL), in JOAG patients, and its association with JOAG severity.

METHODS

A prospective cross-sectional study was conducted from June 2020 until November 2021 involving 3 tertiary ophthalmology centres. The study involved 2 groups of patients which is JOAG groups and control group (age-sex matched). They were grouped into mild, moderate and severe group using modified AGIS scoring system with reliable and reproducible SITA

standard 24-2 Humphrey visual field results. A-scan was performed in order to measure ACD, and AL. AS-OCT was performed to measure CCT.

RESULTS

A total of 120 patients were recruited in this study, whereby 60 patients were included in JOAG group and 60 patients without ocular comorbidities were included in control group. Slightly more male patients 53.3% (n = 32) in JOAG group, and 51.7% (n = 31) in control group. Mean age is 27.97 ± 7.1 in both groups. From the JOAG group, at their first presentation, majority were from severe stage 68.3% (n = 41) followed by early stage 26.7% (n = 16), and moderate stage 5% (n = 3). While at recruitment, majority were from severe stage as well which increased to 70% (n = 42), followed by early stage 16.7% (n = 10), and moderate stage 13.3% (n = 8). We found that statistically significant changes of severity from first presentation and at recruitment ($p < 0.001$). There was significant difference in CCT (556.23 ± 28.93 mm, $p = 0.008$) and AL (25.16 ± 1.63 mm, $p < 0.001$) between JOAG and control group. Multiple linear regression showed that presenting IOP, and AL were associated with severity of JOAG.

CONCLUSIONS

There was a significant mean difference in CCT and AL between JOAG and control groups. There was a significant positive linear relationship between CCT and AL with JOAG. We concluded that presenting IOP and AL were associated with severity of JOAG.

CHAPTER 1
INTRODUCTION

1.0 INTRODUCTION

Glaucoma is defined as a group of condition causing damage to the eye tissue resulting in characteristic optic neuropathy with associated visual field loss. Glaucoma traditionally defined by a triad of signs, including the presence of at least two of the following, which is elevated intraocular pressure, optic disc cupping and visual field loss. According to Quigley and Broman *et al.* 2006, glaucoma is the second leading cause of blindness worldwide after cataract. Glaucoma generally can be classified into primary, secondary and developmental glaucoma. In primary glaucoma, it can be further classified into open angle glaucoma (OAG) and angle closure glaucoma (ACG) according to the configuration of the angle structure. Asia alone accounts for 60% of world's total glaucoma cases (Tham YC *et al.*, 2014). Recent study reported that from 2013 to 2040, South Central Asia will record the steepest increase in number of glaucoma individuals from 17.06 million to 32.90 million compared with other Asian subregions. South-Central Asia is also projected to overtake East Asia for highest overall glaucoma and POAG burden in 2040, while PACG burden remains highest in East Asia (Chan *et al.* 2016). Particularly in Malaysia, as reported in National Eye Survey II, glaucoma is the third leading causes of blindness 6.6%, following cataract and diabetic retinopathy (Chew *et al.*, 2018). Singapore Malay Eye Study in 2008 reported that the prevalence of glaucoma among Malay persons 40 years of age and older in Singapore is 3.4% (Shen *et al.*, 2008)

1.1 Juvenile Open Angle Glaucoma

Juvenile open-angle glaucoma (JOAG) is a subset of primary open-angle glaucoma (POAG), characterized by a pattern of autosomal dominant inheritance. JOAG affecting those who are between 4 and 40 years old, while the adult-onset POAG affecting those older than 40 years. (Thau *et al.*, 2018). Generally, JOAG affects individuals during childhood or early adulthood,

however is distinct from congenital glaucoma that typically presented with buphthalmos, megalocornea, Haab's striae, and ocular or other systemic developmental anomalies.

Aponte *et al.* (2010) reported that the incidence of JOAG was 0.38 per 10,000 residents between 4 and 20 years of age. Prevalence in United States of America was estimated to be 1 in 50000 (Turalba and Chen., 2008).

A study in United States also reported that the economic burden of eye disorders and vision loss among the United States population less than 40 years of age was estimated to be \$27.5 billion per year (Wittenborn *et al.*, 2013). Diagnosed at an early age, with a longer life expectancy of JOAG patients, they require life-long close monitoring to preserve their socially productive status.

1.2 Pathogenesis of JOAG

JOAG has insidious onset. However, it is usually detected late with typically advance optic nerve damage and intraocular pressure of more than 40mmHg. (Adward *et al.*, 1998). JOAG is usually transmitted in an autosomal dominant fashion and most commonly involves the myocilin protein (previously known as trabecular meshwork inducible–glucocorticoid response protein, or TIGR). Based on human in situ studies, the myocilin protein is found in trabecular meshwork cells, trabecular beams, and juxtacanalicular connective tissue. More than 70 identified mutations in the myocilin gene (*MYOC*) which contribute to increased aqueous outflow resistance. Depending on the *MYOC* mutation, various aspects of trabecular meshwork cell function are compromised. Research has shown glaucoma-associated risk stratification based on *MYOC* phenotype: mild risk with the Gln368Stop mutation, intermediate risk with the Thr377Met and Gly252Arg mutations, and severe risk with the Pro370Leu mutation

(Hewitt *et al.*, 2013). However, it is important to note that having an *MYOC* mutation does not necessarily mean that the patient has or will develop JOAG.

Aside from genetic study, a research was done to investigate association of vascular perfusion and structural damage in JOAG patients, using an optical coherence tomography angiography (OCT-A). Abdelrahman *et al.* (2020) reported that there is a strong positive correlation between vessel density and RNFL thickness.

1.3 Intraocular pressure

1.3.1 Glaucoma and intraocular pressure

IOP is the pressure that exerted by aqueous in the eye and its pressure is controlled by following three factors, the rate of aqueous production, resistance encountered in outflow channels and level of episcleral venous pressure (Kanski, 2007).

The normal IOP in the general population ranges from 11-21 mmHg. There is a difference of average IOP among the different races likely due to genetic factors. The mean IOP readings in the Chinese, Malay, and Indian population in Singapore were 14.3 ± 3.1 , 15.3 ± 3.7 , and 15.8 ± 2.9 mmHg respectively. Malay and Indian population on average had 0.81 and 1.43 mmHg higher IOP levels, respectively, than the Chinese (Chua *et al.*, 2014).

IOP higher than 21 mmHg is associated with glaucoma as well as progression of glaucoma. However, there is documented progression of glaucoma even in patients with IOP less than 21 mmHg, which is currently known as NTG. Therefore, fluctuation of IOP is believed to have a more significant role in progression of glaucoma. Normal IOP is affected by time of the day, heart rate, respiration rate and blood pressure (Kanski, 2007). Diurnal variation of IOP curve

showed IOP tend to be higher between 8 am until 12 noon. Fluctuation of IOP more than 5 mmHg is associated with worsening of glaucoma. Therefore, new treatment modalities should aim at reducing the IOP fluctuation (Kanski, 2007).

Strategy to control the sudden drop in ocular perfusion pressure also plays an important role in glaucoma progression. Reduction in ocular perfusion pressure will impair blood circulation to the optic nerve head, thus accentuate the ischaemic process and worsening of nerve fibre layer injury (Moore *et al.*, 2008).

1.3.2 Factors affecting intraocular pressure and glaucoma

Factors affecting IOP and glaucoma include age, race, gender, family history as well as ocular associated factors such as baseline IOP, central corneal thickness (CCT) and vertical cup-disc-ratio (CDR) (Sommer *et al.*, 1991; Tielsch *et al.*, 1995; Gordon *et al.*, 2002; Rudnicka *et al.*, 2006; Fansi *et al.*, 2009). African-Caribbeans in urban setting were associated with higher IOP and thinner CCT (Fansi *et al.* 2009). In a study population, young and healthy Asian-Americans had greater IOP and CDR compared to Caucasians, demonstrating that racial difference do affect the IOP normality (Doss *et al.*, 2014).

Black populations also had the highest prevalence of OAG at all ages; however white populations showed the steepest increase in OAG prevalence with age (Rudnicka *et al.*, 2006). Gender also plays a role in contributing to prevalence of glaucoma, whereby men were found to be more likely than women to have OAG (Rudnicka *et al.*, 2006). Family history with first-degree relative having POAG has adjusted odds ratio of 2.9 in getting POAG (Tielsch *et al.*, 1995).

Blood pressure (BP) showed positive association with POAG with a stronger association among older subjects. Lower perfusion pressure (BP - IOP) was shown to have higher prevalence of POAG as compared to normal perfusion pressure (Tielsch *et al.*, 1995). Diastolic perfusion pressure of lower than 30 mmHg has adjusted odds ratio of 6.2 in getting POAG (Tielsch *et al.*, 1995).

IOP at screening was related to risk of glaucomatous optic nerve damage particularly at levels of 22 to 29 and 30 mmHg and above (Sommer *et al.*, 1991). Myopia had up to three-fold increased risk of glaucoma compared to non-myopic patients, and it was independent of other glaucoma risk factors (Mitchell *et al.*, 1999).

A population-based study also showed cross-sectional association between myopia and high IOP as well as prevalent of glaucoma (Wong *et al.*, 2003). CCT was found to be a powerful predictor for the development of POAG (Gordon *et al.*, 2002). Ocular Hypertension Treatment Study (OHTS) showed that baseline age, vertical CDR, pattern standard deviation, and IOP were good predictors for the onset of POAG (Gordon *et al.*, 2002).

On the contrary, independent predictors of angle closure were female, Chinese ethnicity, shorter axial length and shallower anterior chamber depth (Lavanya *et al.*, 2008). Siblings of patients who were Chinese ethnicity with PAC or PACG have almost a 50% probability of having narrow angles. They were also seven times more likely to have narrow angles than the general population (Amerasinghe *et al.*, 2011).

1.3.3 Measurement of intraocular pressure

Measurement of IOP is utmost important as it is the only modifiable risk factor for progression of glaucoma. Therefore, decision to start or to add topical pressure lowering drugs at times, will depend on whether IOP is properly controlled with antecedent management plan. Similarly, decision for any surgical intervention will also depend on the IOP control. Thus, measurement of IOP is one of the key factors for appropriate management of glaucoma patients. There are several methods used in IOP measurement. It can be divided into indentation and applanation methods. Applanation method can be further subdivided into non-contact or contact techniques (McCafferty *et al.*, 2017).

1.3.3.1 Goldmann applanation tonometry

Goldmann applanation tonometry (GAT) is still the gold standard technique for measurement of IOP. GAT is using Imbert-Fick law (Gloster and Perkins, 1963; Ehlers *et al.*, 1975), which measures the force needed to flatten a fixed area of the cornea. However, variations in corneal properties, such as CCT (Ehlers *et al.*, 1975; Whitacre *et al.*, 1993), corneal curvature (Mark, 1973), hydration (McMillan and Foster, 1975) and rigidity (Brooks *et al.*, 1984) may cause clinically significant inaccuracies in the measurement of IOP. There was a change of 0.28 mmHg of IOP for every 10 μm increase in CCT (Tonnu *et al.*, 2005). Cornea biomechanical factor (cornea hysteresis and cornea resistance factor) also can cause inaccuracy of applanation IOP. Applanation IOP was shown to be significantly correlated with corneal hysteresis and corneal resistance factor (Yu *et al.*, 2012).

1.3.3.2 Other methods of measurement

Pascal dynamic contour tonometry (DCT) is a relatively new method for IOP measurement but with a promising role in the future. It is non-invasive, direct and accurate IOP measurement

irrespective of corneal thickness or corneal elasticity. It is based on direct trans-corneal pressure detection. DCT was reported to have good concordance with intracameral pressure, which is the real IOP (Boehm *et al.*, 2008). Schiøtz tonometry is an older instrument that employs the indentation technique. Schiøtz tonometry is a viable option for IOP measurement due to its compact portability, lower cost and comparable reliability (Chiara *et al.*, 1989). Applanation tonometry devices include the air tonometer, pneumatonograph, tonopen, Perkins and the GAT. Principle of applanation is to flatten a small, fixed area of cornea and measure the resultant pressure. Non-contact tonometry seems to achieve measurement close to GAT measurement (Cook *et al.*, 2012). Applanation pneumotonograph had been shown to correlate well with GAT (Jain and Marmion, 1976). IOP measurement produced almost identical average levels at GAT and Tonopen XL (Ceska *et al.*, 2012). Perkins applanation tonometry yields IOP measurement that is closely comparable with GAT (Arora *et al.*, 2014).

1.4 Central corneal thickness

1.4.1 Definition of central corneal thickness

Cornea is the anterior one-sixth of the outer coat of eyeball. It is transparent and measures about 10.5-11.5 mm horizontally and 9.5-10.5 mm vertically in diameter in adults. The central 4 mm diameter plays an important role for refractive component of our cornea. It is also the area for the measuring of GAT-IOP. Therefore, measurement of CCT is important as it affects the true value of IOP taken. A meta-analysis study showed that 2.5mmHg correlated with a 50 μ m difference from the base CCT (Doughty *et al.*, 2000). An adjusted IOP value conversion table was made according to the pachymeter manufacturer's algorithm based on cannulation study (Ehlers *et al.*, 1975) as shown in Table 1.

Table 1: Correction table used for adjusting IOP based on central corneal thickness (Ehlers *et al.*, 1975)

Central corneal thickness (μm)	Adjustment in Intraocular pressure (mmHg)
445	+7
455	+6
465	+6
475	+5
485	+4
495	+4
505	+3
515	+2
525	+1
535	+1
545	0
555	-1
565	-1
575	-2
585	-3
595	-4
605	-4
615	-5
625	-6
635	-6
645	-7

While IOP can be adjusted based on CCT thickness, there were variations of mean CCT which differs according to population. A study done in California by Badr *et al.* shows mean CCT for African American subjects was $519.9 \pm 42.7 \mu\text{m}$, significantly thinner than the caucasians with

mean CCT of $550.0 \pm 32.8 \mu\text{m}$ (Badr *et al.*, 2017). While mean CCT reading was $552.3 \pm 33.4 \mu\text{m}$ in Chinese, $540.9 \pm 33.6 \mu\text{m}$ in Malays, and $540.4 \pm 33.6 \mu\text{m}$ in Indians ethnicity (Chua *et al.*, 2014). There was 52.8% in Chinese, 68.5% in Malays, and 66.2% in Indians patients that had CCT $< 555 \mu\text{m}$ (Chua *et al.*, 2014).

1.4.2 Factors affecting central corneal thickness

Factors associated with greater mean CCT were younger age, female gender, and diabetes mellitus (Brandt *et al.*, 2001). Topical administration of timolol 0.5% showed a reversible increase in CCT (Grueb and Rohrbach, 2013). Post ocular procedure might cause corneal oedema and cause increase in CCT. Ocular procedure like selective laser trabeculoplasty was reported to have persistent corneal oedema post procedure which results in an increase in CCT (Ozkok *et al.*, 2014).

1.4.3 Measurement of central corneal thickness

CCT has been shown to play an important role in the management of glaucoma. CCT measurements lead to changes in medical therapy (8.5%), laser therapy (2.1%) and surgery decisions (3.2%) of glaucoma patients (Shih *et al.*, 2004). Measurement of CCT can be divided broadly into contact and non-contact methods. Contact method include ultrasonic pachymetry whereas non-contact method such as optical ray path analysis (i.e., Orbscan, Bausch & Lomb), and optical coherence tomography (OCT). Although there was a high correlation among the three methods, ultrasonic pachymetry is the most commonly used method (Fisherman *et al.*, 2005). However, ultrasonic pachymetry requires use of anaesthesia, physical contact and is operator dependent. Reproducibility of ultrasonic pachymetry also depends on precise probe placement (Shildkrot *et al.*, 2005).

Visante anterior segment OCT (OCT, Zeiss) uses coherent light beam reflection at optical interfaces for the imaging of CCT. It is a safe method as it doesn't come into contact with the cornea. It is comparable to ultrasound pachymetry results, although OCT technique has tendency for lower values but it is statistically not significant (Wildner *et al.*, 2007).

1.5 Anterior chamber depth

The anterior chamber is the aqueous humor-filled space inside the eye between the iris and cornea innermost surface, the corneal endothelium (Cassin B, and Solomon S, 1990). In glaucoma, blockage of the trabecular meshwork prevents the normal outflow of aqueous humor, resulting in increased IOP, progressive damage to optic nerve head and eventually blindness. Anterior chamber depth (ACD) varies between eyes, range between 1.5mm to 4.0mm, averaging 3.0mm. It tends to become shallower at older age and eyes with hypermetropia. As depth decreases below 2.5mm, the risk of angle closure glaucoma increases. (Wikipedia, 2022)

1.5.1 Measurement of anterior chamber depth

Determining the ACD is important in estimating risk of angle closure glaucoma. Various methods of measuring ACD, including slit lamp examination, ultrasound, and scheinflug photography. A simpler clinical method quantitatively estimating ACD using a smartphone (EZ ratio) was developed by Dr Ehud Zamir from Centre for Eye Research Australia, the University of Melbourne (Zamir E., 2016)

1.6 Axial length

In new-born, average eyeball is about 16 mm in diameter from front to back. While in infant, the eye grows slightly to a length approximately 19.5mm. the eye will continue to grow,

gradually to the length of about 24 to 25mm (Goldschmidt E., 1969). The axial length (AL) is the distance from corneal surface to an interference peak corresponding to the retinal pigment epithelium or Bruch's membrane (Hitzenberger CK.,1991; Schmid *et al.*, 1996). Majority of AL elongation takes place in the first 3 to 6 months of life, followed by a gradual reduction of growth over the next 2 years, and by 3 years, the adult size is attained (Duke WS., 1970).

Large scale study of ocular components' growth suggested that the eye has reached its adult emmetropic AL by the age of 13 years. Studies also shown that, the anterior chamber has normally reached its maximum depth, and to by crystalline lens its minimum thickness about 15 years of age. Because the crystalline lens decrease in power during slow coordination growth period of eye in childhood (Fledelius HC., 1980; Fledelius HC., 1982).

In the adult, AL remains practically unaltered. A slight but steady change towards hyperopia is the rule, especially after the age of 40 years. Mean adult AL values are 22 to 25mm (Bhardwaj V *et al.*, 2013)

1.6.1 Measurement of axial length

There are 2 main options for measuring AL. Ultrasound biometry and optical biometry. A-scan ultrasound biometry is a more challenging technique to use on children due to the contact nature of the instrument.

1.7 Lens thickness

Crystalline lens thickness (LT) can be affected by different conditions such as aging, presbyopia and myopia (Garcia *et al.*, 2011). After childhood, lens thickness increases linearly by 13 to 29 μm per year (Glasser and Campbell, 1999). Crystalline lens thickening is an important predisposing factor for development of angle-closure glaucoma (Lim *et al.*, 2006). Precise measurement of lens thickness (LT) can be valuable in evaluating this condition.

1.7.1 Lens thickness measurement

A variety of techniques used to measure lens thickness. A-scan ultrasonography (A-scan US) is the reference method for biometric measurement of lens thickness. Accommodation reflex has been shown to increase the variability of A-scan US LT measurements. Proper alignment of probe requires expertise and office measurement can be difficult in young child as well (Lehman *et al.*, 2009). The AS-OCT is another method for obtaining lens thickness. The use of infrared light in the device doesn't change the pupil's size and may hence produce more accurate LT value (Wong *et al.*, 2009).

1.8 White to white distance

White to white (WTW) distance is the horizontal corneal diameter, which was measured between borders of corneal limbus. Traditional clinical application of WTW distance includes diagnosing and managing congenital glaucoma and micro- and megalocornea (Wallace DK and Plager DA., 1996). Currently WTW distance also frequently considered during cataract surgeries, includes variable used in intraocular lens power (IOL) calculation, and is also considered to be a factor influencing corneal astigmatism after cataract surgery (Theodoulidou *et al.*, 2016). WTW distance required for haptic size calculation in angle-supported IOL, anterior chamber IOL, phakic IOL implant, and capsular tension ring (CTR) size (Vass *et al.*, 1999). It is also included in surgical planning for refractive cataract procedures (Han *et al.*, 2019). It is shown that WTW distance is correlated with lens diameter (Dong *et al.*, 2001).

1.8.1 White to white distance measurement

There are several techniques used to measure WTW distance, which can be divided to 2 main groups. Manual using callipers or scales on the slit lamp examination, and automated devices such as ultrasonic biomicroscopy, IOL master, Orbscan II and OCT.

1.9 Morphology features of JOAG

JOAG can be distinguished from congenital glaucoma. Clinically there will be absent of megalocornea, Descemet's breaks or Haab's striae, and anterior segment dysgenesis which are seen in congenital glaucoma (Wiggs *et al.*, 1995; Gupta *et al.*, 2018). Generally open angle, Birla *et al.* (2020) further classify JOAG to several clusters based on iris and gonioscopic features which includes, presence of iris crypt, normal angle, featureless angle, high iris insertion and prominent iris process. Kwun *et al.* (2016) and Elgin *et al.* (2018) reported that JOAG patients showed thinner CCT compare to normal individuals. Several studies also shown that JOAG individuals are myopic with longer axial lengths (Wiggs *et al.*, 1995; Kwun *et al.*, 2016; Elgin *et al.*, 2018).

1.10 Study Rationale

With current understanding of glaucoma, JOAG is seen as a unique group in between primary congenital glaucoma (PCG) and primary open angle glaucoma. Diagnosed at early age, patients with JOAG are expected to have longer life expectancy. They are usually associated with more severe and rapidly progressive disease. However morphologic features in JOAG is not much known as compared to PCG and POAG. There is gap of knowledge in term of early morphologic changes that might occur in JOAG patients before the develop the full-blown glaucoma signs such as visual field changes. By studying the morphologic features of JOAG, this study will help clinician in screening and management of JOAG patients. In term of screening, family members with positive morphologic features particularly will need more frequent follow up. These will help to prevent late diagnosis in such cases. This screening will be the opportunistic screening among positive family members which need to be repeated accordingly if they show certain morphologic changes. In term of management, determining

the features associated with progressing JOAG disease will help clinician to identify JOAG patient who at risk of disease progression which will need for more frequent follow up and more aggressive treatment and management. Moreover, JOAG patient with possible over or under estimation IOP might need different optimal IOP target which dependant to our JOAG patient's central corneal thickness profile. Particularly in JOAG patients whose previous target IOP was achieved but still have a progression of the disease.

CHAPTER 2

LITERATURE REVIEW

2.0 LITERATURE REVIEW

2.1 Central corneal thickness and glaucoma

CCT is important in proper classification of glaucoma whether it is POAG, ocular hypertension (OHT) or NTG. Furthermore, CCT measurement is recommended by the OHTS as it is a predictive factor for conversion of OHT to POAG. Low CCT values are at higher risk of developing POAG up to 70% with decrease of 40 μm in CCT (Whitacre *et al.*, 1993; Gordon *et al.*, 2002). Thus, measurement of CCT could assist to attribute the likelihood of disease diagnosis and progression (Gordon *et al.*, 2002). A thicker CCT will require higher force for applanation, leading to falsely high GAT-IOP. On the contrary, a thinner CCT will give an underestimation of the value of GAT-IOP.

In JOAG particularly, few studies reported to have thinner CCT compared to normal individuals (Elgin *et al.*, 2018; Kwun *et al.*, 2016)

2.2 Anterior chamber depth and glaucoma.

A study done among Caucasians, reported that open angle glaucoma subjects has shallower ACD compared to normal subjects, which also reported in Nigeria. (Tomlinson *et al.*, 1972; Ashaye AO, 2003). Tomlinson *et al.* (1972) suggested that aging crystalline lens may be a major cause of POAG. They also reported LT thicker in open angle glaucoma subjects compare to normal subjects (Tomlinson *et al.*, 1972). Negative correlation between age and ACD was found in glaucoma subjects as reported by Kuzin *et al.* (2010) and Adewara *et al.* (2018). This may be explained by the increased lens thickness with age or movement of the iris lens diaphragm more anteriorly with age.

2.3 Myopia and glaucoma

As myopia was reported to be associated with JOAG, some differences in anterior segment parameters and axial length (AL) are expected in these patients. A study was done to compare the refractive status and anterior segment parameters of patients with JOAG and normal subjects. They concluded that JOAG patients were found to be more myopic than normal subjects (Elgin *et al.*, 2018; Kwun *et al.*, 2016).

Gupta *et al.* (2021) studied the myopia and glaucoma progression among JOAG patients and concluded that JOAG progressors had a greater baseline myopic refraction and a faster myopia development over time. JOAG patient with myopia development could be an indicator of glaucoma progression, hence progressing myopic (≤ -1 D) JOAG patients should be followed up more frequently (Gupta *et al.*, 2021).

Ko *et al.* (2002) compared the risk factors of JOAG and POAG in their study. Myopic refractive state was significantly more common in JOAG than POAG and they stated that axial myopia might be one of the main factors in the pathogenesis of JOAG. Structurally myopic eyes are different from emmetropic eyes. Myopic eyes have longer AL and vitreous chamber depths (Scott and Grosvenor, 1993). Eyes with increased axial length appear to have higher cup–disc ratios (CDRs), increased optic nerve fiber layer defects and possibly greater deformability of the lamina cribrosa. These leads to higher susceptibility to glaucomatous optic disc changes (Fong *et al.*, 1990).

Blue Mountain Eye Study by Mitchell *et al.* (1999) reported the myopia – glaucoma association and has been described in case–control and cross-sectional studies in Europe, Asia, Australia and the USA (Daubs and Crick, 1981; Ponte *et al.*, 1994; Mitchell *et al.*, 1999; Grodum *et al.*, 2001; Yoshida *et al.*, 2001; Wong *et al.*, 2003). Several studies showed that glaucoma risks increased with more severe myopia. The odd ratio of glaucoma for moderate myopia was 3.3

in the Blue Mountains Eye study of 3654 adults, while glaucoma rates increased with increasing myopia in logistic regression models in 32 918 Swedes (Mitchell *et al.*, 1999; Grodum *et al.*, 2001). Yoshida *et al.* (2001) reported positive associations between the strength of myopic refraction and the prevalence of OAG for specific age-gender groups, in 64,394 Japanese. Despite increasing in myopia prevalence, the risk factors that lead to its progression are still not fully known. There are numbers of pharmacological and optical treatment that have been used to help slow the progression of myopia. Medications such as 0.01% atropine are affective agents in reducing myopia progression, however effects of long-term usage of topical anti muscarinic drugs in children remain unclear. Orthokeratology (OK) is an optical treatment option using specially designed reverse geometry contact lens that are worn overnight (Hiraoka *et al.*, 2018).

2.4 Anterior segment parameters in glaucoma.

Most of previous studies suggested that moderate to high myopia is associated with increased risk of POAG (Knapp *et al.*, 1925; Podos *et al.*, 1966), low-tension glaucoma, and ocular hypertension (Abdalla *et al.*, 1970; Perkis *et al.*, 1982; and Daubs *et al.*, 1981). Shamira *et al.* (2010) in The Singapore Malay Eye Study 2010, conclude that there is an association between moderate and high myopia and longer AL, and POAG. Axial myopia is suggested as a potential risk factor for POAG. Gordon *et al.* (2002) reported in Ocular Hypertension Treatment Trial ,2002, that CCT is a significant risk factors in development of POAG. CCT retained its statistically significant as predictor of glaucoma development, with hazard ratio 1.82 for each 40 μm thinner CCT.

While in primary angle closure glaucoma (PACG) eyes, following anatomical features is usually seen such as small cornea, shallow ACD, thick lens, anterior lens position, and short AL (Lowe *et al.*, 1970; Lee *et al.*, 1984; Marchini *et al.*, 1998).

In JOAG particularly, was described to be associated with myopic refractive state (Kwun *et al.*, 2016). Elgin *et al.* (2018) reported that more myopic shift, longer AL and thinner CCT value in JOAG. However, there is a limitation in number of reports pertaining to anterior segment parameters of JOAG.

CHAPTER 3

OBJECTIVES

3.0 RESEARCH OBJECTIVE

3.1 General Objective

To compare CCT, ACD, and AL between JOAG patients and controls.

3.2 Specific Objectives

- 1) To compare CCT between JOAG patients and controls.
- 2) To compare ACD between JOAG patients and controls.
- 3) To compare AL between JOAG patients and controls.
- 4) To determine the association between CCT, ACD, and AL with severity of JOAG.

3.3 RESEARCH QUESTIONS

- 1) Are there any differences in CCT, ACD, and AL between JOAG and normal subjects?
- 2) Are there any associations between CCT, ACD, and AL with severity of JOAG?

3.4 RESEARCH HYPOTHESIS

- 1) There are differences in CCT, ACD, and AL between JOAG and normal subjects.
- 2) There are association between CCT, ACD, and AL with severity of JOAG.

CHAPTER 4

RESEARCH METHODOLOGY

4.0 METHODOLOGY

4.1 Study Design

A cross sectional study was conducted in Ophthalmology Clinic, Hospital Sultanah Bahiyah (HSBAS), Alor Setar, Ophthalmology Clinic, Hospital Raja Perempuan Zainab II (HRPZ II), Kota Bharu, and Ophthalmology Clinic, Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, from March 2020 until November 2021. The study population involved JOAG patients attending Ophthalmology Clinic at HSBAS Alor Setar, Kedah, HUSM Kubang Kerian, Kelantan, and HRPZ II Kota Bharu, Kelantan during the study and fulfilled selection criteria.

4.2 Ethical Approval

The study was conducted after approval by the local Human Research Ethical Committee (Universiti Sains Malaysia [usm])/Jawatankuasa Etika Penyelidikan Manusia (JEPeM). The study protocol code was USM/JEPeM/20100522 (Appendix A). The committee is according to the study protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) – Harmonised Tripartite Guideline for Good Clinical Practice (GCP). This study was also approved by Ethical & Medical Research Committee (Jawatankuasa Etika & Penyelidikan Perubatan) of Ministry of Health (MOH), Malaysia with registration number of NMRR-20-520-54291.