EFFECT OF CIGARETTE SMOKING AND PHYSICAL ACTIVITY ON THE SEVERITY OF PRIMARY ANGLE CLOSURE GLAUCOMA IN MALAY PATIENTS

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

Dated 27/03/2017   ……………………….........

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ABSTRAK

PENGENALAN

Penyakit glaukoma adalah penyebab kebutaan kekal terbesar di dunia, di mana penduduk Asia menyumbang kepada separuh dari bilangan kes-kes glaukoma tersebut. Glaukoma sudut terbuka primer merupakan jenis glaukoma yang paling lazim tetapi glaukoma sudut tertutup primer merupakan bilangan yang lebih banyak di rantau Asia. Penyakit glaukoma ini kebiasaannya progres ke tahap lebih teruk; walaupun tekanan intraokular adalah terkawal. Faktor-faktor yang menyebabkan penyakit ini progres terbahagi kepada; faktor boleh ubah dan tidak boleh ubah. Faktor boleh ubah termasuk amalan merokok and aktiviti fisikal. Walaupun terdapat beberapa bukti saintifik tentang hubung kait antara amalan merokok dan aktiviti fisikal ke atas penyakit glaucoma, tetapi tiada kajian yang berkaitan dengan tahap keterukkan penyakit ini.

OBJEKTIF

Kajian ini adalah bagi menilai hubung kait di antara amalan merokok dan aktiviti fisikal dengan tahap keterukan penyakit glaukoma sudut tertutup primer di kalangan pesakit berbangsa Melayu.

KAEDAH KAJIAN

Satu kajian rentas telah dijalankan yang melibatkan pesakit glaukoma sudut tertutup primer di antara April 2014 dan Ogos 2016 di klinik mata: Hospital Universiti Sains Malaysia (HUSM), Hospital Raja Perempuan Zainab II (HRPZ II), Hospital Kuala Lumpur (HKL), Hospital Sultanah Bahiyah (HSB) and Hospital Sultanah Nur Zahirah (HSNZ). Hanya pesakit glaukoma yang berbangsa Melayu dan dapat melakukan ujian medan penglihatan menggunakan analisis

Humphrey visual field 24-2 yang tepat secara berulang sekurang-kurangnya dua kali, telah dipilih. Tahap keterukan penyakit glaukoma adalah berdasarkan sistem skor 'Advance Glaucoma Interventional Study' (AGIS) yang telah dimodifikasi, ke atas ujian medan penglihatan. Tahap keterukan glaukoma ini terbahagi kepada ringan, sederhana dan teruk.

Setiap subjek ditemuramah mengenai amalan merokok dan aktiviti fisikal oleh penyelidik utama secara bersemuka. Amalan merokok dan perinciaan berkenaan merokok adalah berdasarkan soalan kajiselidik "Singapore Malay Eye Study" (SiMES). Status perokok terbahagi kepada perokok aktif, perokok lama, perokok pasif, dan bukan perokok. Tempoh merokok dan bilangan rokok yang diambil dalam sehari turut direkodkan. Penilaian terhadap tahap aktiviti fisikal dibuat berdasarkan soalan kajiselidik "International Physical Activity Questionnaire (IPAQ)" yang telah divalidasikan ke dalam Bahasa Malaysia. Tahap aktiviti fisikal terbahagi kepada aktiviti ringan, sederhana dan aktiviti berat. Pengiraan kadar tenaga yang digunakan (METs) turut dikira berdasarkan jenis dan kekerapan aktiviti fisikal selama 7 hari sebelum temuramah dijalankan.

Analisa univariasi telah dibuat bagi memeriksa setiap faktor-faktor yang mempengaruhi tahap keterukan penyakit glaukoma ruang tertutup. Kaitan dan hubung kait antara amalan merokok dan aktiviti fisikal terhadap skor AGIS dibuat menggunakan "multiple linear regression" (MLR).

KEPUTUSAN

Seramai 150 pesakit glaukoma sudut tertutup primer (50 glaukoma ringan, 50 sederhana dan 50 teruk) terlibat dalam kajian ini. Terdapat hubung kait yang signifikan di antara amalan merokok dan tahap keterukkan penyakit glaucoma (p = 0.044). Bilangan rokok yang dihisap turut menunjukkan hubung kait yang signifikan dengan tahap keterukkan penyakit glaukoma.

Tetapi tempoh merokok (dalam kiraan tahun) tidak menunjukkan hubung kait yang signifikan dengan tahap keterukkan penyakit glaukoma. Bilangan rokok yang dihisap meningkatkan skor AGIS sebanyak 0.7 (ubahan b 0.65, 95% CI 0.27, 1.03, $p = 0.001$).

Tahap aktiviti fisikal dan tahap keterukan glaukoma juga menunjukkan hubung kait yang signifikan ($p < 0.001$). Aktiviti fisikal menunjukan perkaitan linear yang negatif yang signifikan dengan skor AGIS. Peningkatan aktiviti fisikal mengurangkan skor AGIS sebanyak 3.4 (ubahan b -3.41, 95% CI -5.23, -1.59, $p < 0.001$).

KESIMPULAN

Amalan merokok dan aktiviti fisikal merupakan faktor risiko boleh ubah bagi tahap keterukan penyakit glaukoma sudut tertutup primer. Pengurangan atau berhenti merokok dan peningkatan aktiviti fisikal berpotensi untuk mengurangkan risiko peningkatan tahap keterukan penyakit glaukoma. Amalan hidup sihat di kalangan pesakit glaukoma dapat membantu dalam mengurangkan kerosakan saraf optik.

ABSTRACT

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide, with Asians accounting for approximately half of the world's glaucoma cases. Primary Open Angle Glaucoma is the most common form of glaucoma but Primary Angle Closure Glaucoma (PACG) constitute a higher number of cases in Asia. Progression of glaucoma is common; despite good control of intraocular pressure (IOP). Risk factors associated with progression of glaucoma can be non-modifiable or modifiable. Research on identification of modifiable risk factors are scarce. Modifiable risk factors include cigarette smoking and physical activity. There are limited evidences on the potential association between cigarette smoking and physical activities on the development, progression, and severity of PACG.

OBJECTIVE

To determine the association between cigarette smoking and physical activity on the severity of primary angle closure glaucoma (PACG) in Malay patients.

METHODOLOGY

A cross-sectional study was conducted between April 2014 and August 2016 involving five ophthalmology clinics in Malaysia: Hospital Universiti Sains Malaysia (HUSM), Hospital Raja Perempuan Zainab II (HRPZ II), Hospital Kuala Lumpur (HKL), Hospital Sultanah Bahiyah (HSB) and Hospital Sultanah Nur Zahirah (HSNZ). Only Malay patients who were able to provide two consecutive reliable and reproducible Humphrey Visual Field (HVF) 24-2 analyses were included. Severity of glaucoma was based on modified Advanced Glaucoma

Intervention Study (AGIS) scoring system on HVF and categorised into mild, moderate and severe glaucoma.

Face to face interview was conducted to assess their smoking habits and physical activities. Their smoking status was obtained using validated questionnaires from Singapore Malay Eye Study (SiMES). Cigarette smoking was divided into active smoker, ex-smoker, passive smoker and non-smoker. Duration of smoking and number of cigarette smoked per day was documented. Physical activity status was assessed using validated Bahasa Malaysia version of International Physical Activity Questionnaire (IPAQ). Based on their physical activities over the past 7 days, PACG patients was categorised into mild, moderate and heavy physical activity. The duration of physical activity and measurement of energy requirement (METs) was also calculated.

Univariate analysis was conducted to examine other risk factors for severity of glaucoma and AGIS score. The association of smoking and physical activity with AGIS score was analysed using multiple linear regression (MLR).

RESULTS

A total of 150 Malay patients were recruited (50 with mild, 50 with moderate and 50 with severe glaucoma). There was significant association between cigarette smoking and severity of glaucoma ($p = 0.038$). A significant association was also seen between the number of cigarette smoked and severity of glaucoma ($p = 0.044$). However, there was no significant association in duration of smoking (in years) with severity of glaucoma. Smoking do not appear to increase the AGIS score significantly but every increase in number of cigarette smoked increases the AGIS score by 0.7 (adjusted b 0.65, 95% CI 0.27, 1.03, $p = 0.001$).

There was significant inverse relationship between physical activity and AGIS score. Every increase in physical activity reduces the AGIS score by 3.4 (adjusted b -3.41, 95% CI -5.23, -1.59, p < 0.001).

CONCLUSION

Cigarette smoking and physical activity are potential modifiable risk factor for severity of PACG. Cessation of cigarette smoking may help in halting the progression of glaucomatous visual field defect. Physical activity may protect against having more severe glaucoma. It is recommended that PACG patients practice healthier lifestyle to prevent progression of PACG.

Chapter 1
Introduction

1.1 GLAUCOMA

Glaucoma is a group of chronic progressive optic neuropathies characterised by slow progressive degeneration of the retinal ganglion cells and their axons, resulting in a specific appearance of the optic disc (structural) with corresponding pattern of visual loss (functional) (Weinreb & Khaw, 2004). The structural changes of optic nerves include excavation or cupping of the optic disc, thinning of the neuroretinal rim resulting in increased vertical cup-disc ratio (VCDR) and retinal nerve fibre layer (RNFL) defects. This is due to the loss of retinal ganglion cells and their axons as well as deformation of connective tissues supporting the optic disc (Burgoyne CF et al, 2005; Quigley HA, 2011). These structural changes lead to functional defects; progressive visual field defect (Yucel YH et al, 2001; Quigley HA, 2011).

Glaucoma can be classified into two main groups according to the angle structure; closed angle glaucoma and open angle glaucoma (Coleman AL, 1999; Glaucoma Research Foundation, 2012). Open and closed angle glaucoma can further be classified into primary or secondary glaucoma. Primary glaucoma, of open angle category includes Primary Open Angle Glaucoma (POAG), Juvenile Open Angle Glaucoma (JOAG), Normal Tension Glaucoma (NTG) and congenital glaucoma (Glaucoma Research Foundation, 2012). The most common type may differ from one region of the world to another. For instance, Primary Angle Closure Glaucoma (PACG) is more prevalent in certain regions in Asia, whereas POAG is more equally distributed throughout the world and is the most common form of the disease (Quigley HA, 1996).

1.2 PRIMARY ANGLE-CLOSURE GLAUCOMA

The current classification of PACG is based on International Society of Geographical and Epidemiological Ophthalmology (ISGEO) definitions for glaucoma which was agreed on by the World Glaucoma Association (WGA) (Foster PF et al, 2002; Foster P et al, 2006). This classification places emphasis on evidence of glaucomatous optic neuropathy together with gonioscopic evidence and can be classified into three types; Primary angle closure suspect (PACS), Primary angle closure (PAC) and PACG. PACS is defined as an eye in which 180° or more appositional contact between the peripheral iris and posterior trabecular meshwork is considered possible with normal IOP, no peripheral anterior synechiae (PAS) and no evidence of glaucomatous optic neuropathy (GON). PAC is defined as an eye with 180° or more occludable drainage angle and features indication that trabecular obstruction by the peripheral iris has occurred, such as raised IOP of more than 21 mmHg, PAS, iris whirling, "glaucomflecken" lens opacities, or excessive pigment deposition on the trabecular surface in the absence of GON. The term PACG is used to indicate PAC eyes with GON (Foster PJ et al, 2002; Foster P et al, 2006; European Glaucoma Society, 2014).

GON can be classified according to three levels of evidence. Category 1, which provide the highest level of certainty, requires optic disc abnormalities (VCDR > 97.5th percentile of the normal population) and visual field defect consistent with glaucoma. In Category 2, if the visual field test could not be performed due to advanced loss of vision, glaucoma can be diagnosed on the basis of a severely damaged optic disc (VCDR > 99.5th percentile of the normal population). Lastly in Category 3, if the optic disc could not be visualized due to media opacity, a visual acuity < 3/60 and either IOP exceeding the 99.5th percentile of the normal population,

or evidence of previous glaucoma filtering surgery, would be sufficient to make the diagnosis (Foster PJ et al, 2002; Foster P et al, 2006).

A majority of those with PACG presents as a chronic, asymptomatic form while the acute, symptomatic ones are seen in less than 25% of cases (Foster PJ et al, 2002; Quigley HA, 2011). Acute primary angle closure (APAC) is commonly considered as an ophthalmic emergency. It can present with the following symptoms including ocular or periocular pain, frontal headache on the side of affected eye, nausea and/or vomiting, a previous history of intermittent blurring of vision with haloes (Aung T et al, 2001; Glaucoma Research Foundation, 2012; European Glaucoma Society, 2014) and may be accompanied by the following signs such as conjunctival injection, corneal epithelial edema, mid-dilated unreactive pupil, and shallow anterior chamber (Aung T et al, 2001). Investigations will show raised IOP and presence of an occluded angle in the affected eye by gonioscopy (Aung T et al, 2001).

1.2.1   Epidemiology of Primary Angle Closure Glaucoma

According to a survey by the World Health Organization (WHO) in 2010, the approximated number of people visually impaired in the world is 285 million out of which 39 million are blind and 8% of all blindness is contributed to glaucoma (World Health Organization, 2012). Glaucoma is the second leading cause of blindness worldwide (Quigley & Broman, 2006; World Health Organization, 2012). Globally, an estimated 60.5 million people suffered from glaucoma in 2010 (Quigley & Broman, 2006). Of these, an approximated 44.7 million had POAG and 15.8 million PACG (Quigley & Broman, 2006). The prevalence of glaucoma is expected to reach 79.6

million in 2020 with 58.6 million and 21 million of POAG and PACG respectively (Quigley & Broman, 2006).

Based on a latest systemic review and meta-analysis, the overall prevalence of glaucoma for the population aged 40 to 80 years was 3.54% of which 3.05% was attributed by POAG and 0.50% by PACG in 2013 (Tham YC et al, 2014).

A larger proportion of women are affected by glaucoma as seen in 59.1% of all people with glaucoma, 55.4% of OAG and 69.5% of ACG (Quigley & Broman, 2006). Women bear a greater burden than men because not only do women have a longer lifespan, but women also outnumber men (National Center for Health Statistics, 2009; Vajaranant TS et al, 2010; Central Intelligence Agency, 2016). Glaucoma being a disease of longevity, hence more women are seen to be affected.

Bilateral blindness is seen in 3.9 million people with ACG in 2010, rising to 5.3 million people in 2020 (Quigley & Broman, 2006). Although only 24% of those with primary glaucoma have ACG, the amount of ACG blind is nearly identical to that of OAG due to the greater estimated morbidity of this disease (Quigley & Broman, 2006).

Asia constitutes for a disproportionately higher number of PACG as opposed to the number of POAG cases which are more evenly distributed throughout the world (Quigley HA, 1996). Hence, the prevalence varies across geographical regions with the highest prevalence of PACG being Asia (1.09%; 95% CI, 0.43-2.32) (Tham YC et al, 2014). Based on the prevalence models by Quigley and Broman (2006), in 2010 higher prevalence of PACG cases are seen in Asian countries; China 1.26%, Southeast Asia 1.20%, India 0.80%. However, the prevalence of PACG in Japan and Middle East are

estimated to record lower than average; 0.39% and 0.16% respectively (Quigley & Broman, 2006). Therefore, Asians represents 87% of the 15.7 million with ACG (Quigley & Broman, 2006).

1.2.2 Prevalence of Primary Angle Closure Glaucoma in Malay populations

Asians are a heterogenous population, a melting pot. It is no surprise that there is variation in disease prevalence among Asian population. Various epidemiologic population-based studies in East Asia and Southeast Asia shows variation in the prevalence of PACG; Chinese 1.3% (He M et al, 2006), Mongol 1.4% (Foster PF et al, 1996), Thai 0.9% (Bourne RR et al, 2003), Nepal 0.39% (Thapa SS et al, 2012). Numerous population based studies conducted across India showed the prevalence of PACG ranges between 0.29% to 4.3% (Jacob A et al, 1998; Dandona L et al, 2000; Ramakrishnan R et al, 2003; Raychaudhuri A et al, 2005; Vijaya L et al, 2006, Palimkar A et al, 2008).

Malays account for 5% of the world's population. Although there are approximately 300 million to 400 million people of Malay ethnicity living in Asia (Population Reference Bureau, 2016), the burden, causes, risk factors and epidemiology of blinding eye diseases in this ethnic group are surprisingly lacking. Most knowledge about eye disease has been derived from Chinese, Japanese and Indian population, but little knowledge is known in Malay population.

According to the data released by the Department of Statistics, Malaysia, the population of Malaysia was 28,334,135, making it the 42nd most populated country. The population

of Malaysia consists of many ethnic groups. Malays make up the majority with 50.4% of the population, while indigenous ethnic groups (known as Bumiputera) make up another 11% (Population Distribution and Basic Demographic Characteristics 2010. Department of Statistics, Malaysia).

Based on the Singapore Malay Eye Study (SiMES), a population based study that screened 3280 Malay participants residing in Singapore, aged 40 to 80 years, the prevalence of PACG in Malays is 0.12% (Shen SY et al, 2008). In Malaysia, glaucoma emerged as the fifth leading cause of both blindness and low vision based on the National Eye Survey 1996 (Zainal M et al, 2002). This represents to roughly 1.8% of all bilateral blindness and 1.8% of all low vision in our country's population (Zainal M et al, 2002). Whilst the number is much smaller compared to cataract (39.1% of blindness and 39.5% of low vision) and refractive error (4.1% of blindness and 48.3% of low vision), the results of the survey should not be taken at face value. This is because the sample size of 18,027 participants was too small for subgroup analysis for the results to be representative of the country's population. In addition, poor response rate of 69% may sway the results to certain causes. Furthermore, the examination was done at the respondent's home with no access to slit lamp examination, gonioscopy or visual field assessment. Glaucoma was also poorly defined as presence of horizontal cup-disc ratio of 0.4 or more with an IOP of 22 mmHg or more, taken with a Perkins tonometer. All these factors contribute to the underestimation of the prevalence of glaucoma. It is therefore likely that the figure reported by Zainal et al (2002) is only the tip of the iceberg. Currently, there are no statistics on prevalence of glaucoma in Malaysia (Clinical Practice Guidelines, 2008).

1.3   GLAUCOMA PROGRESSION AND SEVERITY

Glaucoma is a chronic progressive disease resulting in optic nerve head damage that requires lifelong monitoring (Brusini and Johnson, 2007). Glaucomatous damage can be quantified using either structural (changes in the optic nerve and RNFL) or functional loss (visual field defects), or a combination of both (Brusini and Johnson, 2007; Medeiros FA et al, 2012a). The rate of progression varies highly among patients (Leske MC et al, 2007, Rossetti L et al, 2010). Disease progression in glaucoma is common and despite treatment, majority of patients still progress (Rossetti L et al, 2010).

1.3.1   Progression of Primary Angle Closure Glaucoma

Based on a retrospective hospital based study, the incidences of progression from PACS to PAC, PACS to PACG, PAC to PACG and, mild and moderate PACG to advanced PACG were 14%, 11.5%, 19.0% and 33% respectively in Malays after at least 5 years of follow up (Liza-Sharmini AT et al, 2014a). The incidence of progression from PACS to PAC and PAC to PACG were lower when compared to a prospective study on the Indian population; 22% and 28.5% respectively (Thomas R et al, 2003a; Thomas R et al, 2003b). The difference between the two studies may be attributed to the differences in the methodology, where prospective study can provide a more accurate outcome compared to a retrospective one.

The presence of APAC seems to protect against the progression towards development and progression of glaucomatous optic neuropathy to a certain extend (Ang LPK et al, 2004). Only 17.5% of symptomatic eyes (history of APAC) developed end stage VF

defects. In contrast, 52.8% of eyes without history of APAC (asymptomatic) developed end-staged VF defects at initial presentation (Ang LPK et al, 2004). Similar finding was observed in Malay patients; 15% of asymptomatic angle closure were blind and 30.5% were at an advanced stage of glaucoma (Liza-Sharmini et al, 2014a). The severity of VF defects in PACG patients could be due to the asymptomatic nature of the disease similar to POAG (Lee YH et al, 2004, Chakrabarti S et al, 2007). The presence of APAC may create better awareness that lead to earlier detection of the disease but do not prevent against progression of the disease; 33% of eyes with APAC progressed to develop glaucomatous changes (Liza-Sharmini et al, 2014a). In addition, lack of awareness and poor health care system may also play a role in late presentation of PACG (Eke T et al, 1999; Saw SM et al, 2003; Hennis A et al, 2007; Altangerel U et al, 2009). Deficiency of awareness may be due to increasing age, lack of formal education, unemployment, illiteracy and poor accessibility to health care system (Saw SM et al, 2003).

1.3.2 Monitoring glaucoma progression

In clinical practice, monitoring of disease progression is done using serial evaluation of longitudinal series of visual field (functional) measurements (Kirwan JF et al, 2014, Saunders LJ et al, 2014). Standard automated perimetry (SAP) is the most common method for assessing VF in glaucoma and has been widely used for many years (Heijl A, 1989; Chauhan BC, 2008). SAP can be used to measure the rate of glaucoma progression (Chauhan et al, 2008). The European Glaucoma Society also recommended SAP as the measuring tool for progression in clinical practice (European Glaucoma Society, 2014).

The progression of glaucoma can also be monitored by the structural changes of the optic nerve head (ONH). With the advancement of technology, newer and more sophisticated ophthalmic imaging devices have been introduced such as, Heidelberg retinal tomograph (HRT) and optical coherence tomograph (OCT). These non-invasive imaging tools provide us with quantitative images and allows for precise observation, documentation and monitoring of the ONH, RNFL and inner macular layer (Medeiros FA et al, 2012b; Kirwan JF et al, 2014). However, it is important to not establish progression of glaucoma solely on quantitative images alone but to determine progression on the agreement and correspondence between structural progression and functional deterioration (Musch DC et al, 2009; Leung CKS et al, 2011; Kirwan JF et al, 2014).

1.3.3 Evaluation of visual field progression

1.3.3.1 Trend-based Analysis

Currently, evaluation of visual field progression can be done using trend-based analysis and event-based analysis of SAP (Birch MK et al, 1995; Spry and Johnson, 2002; Heijl A et al, 2002; Diaz-Aleman VT et al, 2009). Trend-based analysis is based on the rate of progression of the visual function of the eye through a linear regression model using a new global index; visual field index (VFI) (Casas-Llera P et al, 2009; Rao HL et al, 2013). The VFI is the gross percentage of visual function for a given field at each point where the visual thresholds are estimated. VFI is calculated from pattern deviation (PD) plots in eyes with mean deviation (MD) of better than -20 dB and from total deviation plots in eyes with MD worse than -20 dB (Rao HL et al, 2013). Central visual field points are more heavily weighted, therefore trend-based analysis becomes more

sensitive to detect change in visual field that are more severely abnormal (Giraud JM et al, 2010). VFI analysis was also found to be more accurate than the traditional MDI analysis for determining rate of progression and is considerably less affected by cataract or cataract surgery (Bengtsson and Heijl, 2008). Major limitations of trend-based analysis are the length of follow-up and the number of HVF test required to detect progression (Caprioli J, 2008; Rao HL et al, 2013). In general, VFI trend-based analysis take longer to detect progression but do so with higher specificity, and they become more useful as the disease becomes more severe (Giraud JM et al, 2010; Rao HL et al, 2013).

1.3.3.2 Event-based Analysis

The event-based analysis is essentially to detect the occurrence of progression at certain point (Caprioli J, 2008). Glaucoma progression analysis (GPA) software incorporated in Humphrey Visual Field Analyser (HVA) (Carl-Zeiss Meditec, Dublin, CA) is an example of event-based analysis (Casas-Llera P et al, 2009). GPA uses statistical criteria designed for the Early Manifest Glaucoma Trial to detect progression of VF defects (Leske MC et al, 1999). When the pattern deviation probability maps show a significant deterioration at the same three or more points on two consecutive follow-up test, the GPA will detect this as "possible progression"; if significant deterioration is seen at the same three or more points in three consecutive follow-up tests, GPA shows this as "likely progression". The software flags as "no progression detected" if the above two criteria are not met (Rao HL et al, 2013). Nouri-Mahdavi K et al compared GPA with VFI and Advanced Glaucoma Intervention Study (AGIS) method in predicting VF progression and found that GPA predicted outcomes better (Nouri-

Mahdavi K et al, 2007). The event-based GPA analysis is capable of detecting progression earlier compared to trend VFI analysis by 7 months (Casas-Llera P et al, 2009). A primary limitation of event-based analysis is in detecting progression of defect in the central 10 degrees (Diaz-Aleman VT et al, 2009; Arnalich-Montiel F et al, 2009). Hence, event-based analyses are more likely to detect progression earlier and are more sensitive ((Nouri-Mahdavi K et al, 2007; Casas-Llera P et al, 2009).

1.3.4   Staging the severity of glaucoma

Staging the severity of glaucoma enhances the management of the glaucoma towards individualized treatment (Susanna Jr. and Vessani, 2009). It is therefore essential to standardize the glaucoma severity scoring to provide a common understanding for both clinical and research purposes (Susanna Jr. and Vessani, 2009). The staging of glaucomatous damage can be classified into mild, moderate, and advanced or severe based on either structural or functional loss criteria, or a combination of both (Susanna Jr. and Vessani, 2009).

The most common method used to quantify glaucomatous damage is using serial HVF evaluation (Brusini and Johnson, 2007). At baseline, it detects and quantifies damage, and in subsequent follow-up of a glaucoma patient, it detects stability or progression of the disease over a period of time (Susanna Jr. and Vessani, 2009). To quantify the severity of glaucomatous damage using analysis of structural damage to the ONH and RNFL is still under evaluation (Brusini and Johnson, 2007).

Various staging systems using SAP have been proposed such as Aulhorn and Karmeyer's classification (Greve E, 1982; Brusini and Johnson, 2007); Functional Vision Score system (Colenbrander A et al, 1992); Quigley's Grading scale (Quigley HA et al, 1996); Hodapp-Parrish-Anderson (HPA) classification (Hodapp E et al, 1993); Glaucoma Staging System (GSS) (Brusini P, 1996); Advanced Glaucoma Intervention Study (AGIS) (Investigators AGIS, 1994).

1.3.4.1 Hodapp-Parrish-Anderson (HPA) classification

HPA classification system considers two criteria: the overall extent of damage and on the defect(s) proximity to the fixation point (Susanna Jr. and Vessani, 2009). HPA uses both the mean deviation (MD) value and the number of defective points in the Humphrey Statpac-2 pattern deviation probability map of the 24-2 on SITA-standard HVF analysis (Susanna Jr. and Vessani, 2009). This classification is popular due to the ease in assessment. However, HPA characterized the visual field defect into four relatively course stages and does not give information about the location and depth of the defect(s) (Susanna Jr. and Vessani, 2009). In addition, it requires an accurate and time-consuming analysis of every single visual field result (Brusini and Filacorda, 2006).

1.3.4.2 Advanced Glaucoma Intervention Study (AGIS) staging

A continuous glaucoma staging systems has been recommended by the Advanced Glaucoma Intervention Study (AGIS). In this scoring system, severity of glaucoma can be quantified using the Humphrey 24-2 threshold test. The AGIS visual field defect

score is based on the number and depth of clusters of adjacent depressed test sites in the upper hemifield, lower hemifield and in the nasal area of the total deviation plot (an event-based analysis) (Investigators AGIS, 1994; Ng M et al, 2012). The scores for each hemifield and nasal area are summed up and visual field scores are divided into five categories: 0 = normal visual field; 1-5 = mild damage; 6-11 = moderate damage; 12-17 = severe damage; and 18-20 = end stage (Investigators AGIS, 1994). This staging system provide standardized classification of visual field according to severity (Nouri-Mahdavi K et al, 2004). Thus, it is very useful for scientific and clinical research. However, it is time-consuming, requires special training and not practical for day-to-day clinical usage (Brusini and Johnson, 2007).

1.3.4.3 Glaucoma Staging System (GSS)

The GSS is a modified version of the HPA system. It is based on MD and Corrected Pattern Standard Deviation (CPSD) values, the location and number of points depressed on the pattern deviation plot, the Glaucoma Hemifield Test (GHT) from HVF and plot the values on a Cartesian coordinate diagram (Brusini and Johnson, 2007; Ng M et al, 2012). Stage of glaucoma damage can be determined by the intersection of MD and CPSD values on the diagram. GSS has a total of 6 stages: Stage 0 (normal visual field); Stage 1 (early field defect); Stage 2 (moderate field defect); Stage 3 (advanced field defect); Stage 4 (severe field defect) and Stage 5 (end-staged disease) (Ng M et al, 2012). GSS not only provide information of stage of glaucoma damage but the type of damage sustained whether generalized, mixed or focal. GSS is quick and able to provide the specific visual field damage (Koçak I et al, 1997). However, GSS is unable to provide information on location, shape or morphology of the visual field defects.

1.3.4.4 Enhanced Glaucoma Staging Score

Enhanced GSS (e-GSS) is a modified and improved system of GSS (Brusini and Filacorda, 2006). The major limitations of GSS; non-mutually exclusive criteria between stages (narrow band between Stage 0 and Stage 1) which may result in some fields classified ambiguously, and the need to recalculate the PSD values, if corrected indices are not available (Brusini and Filacorda, 2006). There was a strong association between e-GSS and AGIS and HAP systems in staging the severity of glaucoma (Brusini and Filacorda, 2006). There was also a good correlation of e-GSS with a classification based on the Bebié curve (Brusini and Filacorda, 2006).

1.4 RISK FACTORS FOR PROGRESSION AND SEVERITY OF PRIMARY ANGLE CLOSURE GLAUCOMA

PACG is known to cause more blindness compared to POAG. Identification of factors affecting the progression and severity of PACG is essential, to prevent further acceleration of the disease. However, there is minimal knowledge on the factor affecting progression and severity of PACG. Various studies focused on the risk factors affecting development of PACG (Senthil S et al, 2008; Garudadri C et al, 2010; Li and Cui, 2012, Hsu WC et al, 2014). The risk factors can be divided into non-modifiable and modifiable risk factors.

Advancing age is a known non-modifiable risk factor for developing PACG (Drance SM, 1997). This is evident by numerous population-based prevalence studies carried out globally (Foster PJ et al, 2000; Dandona L et al, 2000; Buhrmann RR et al, 2000; Bonomi L et al, 2000; Baskaran M et al, 2015). The prevalence of PACG in a rural southern Indian population showed that the odds for PAC and PACG increased with age after adjusting for sex (Vijaya L, 2006). The prevalence of PACG for the age group 40 to 49 years was 0.63% (95% CI, 0.24 to 1.01) and increased to 2.97% (95% CI, 1.72 to 4.23) for those 70 years and above (Song WL et al, 2011).

Age is also identified as a risk factor for progression of PACG. For each year increase in age increases the risk of disease progression by 1.02 folds (95% CI, 0.98 to 1.06) in Malay patients with PACG (Liza-Sharmini AT, 2014a). Studies by Thomas R et al reported the 5-year incidence of PACS progressing to PAC was 22% and PAC progressing to PACG was 28.5% (Thomas R et al, 2003a; Thomas R et al, 2003b, Sihota R, 2011).

As discussed earlier, race is another risk factor for PACG. PACG is approximately three times more common in Asians compared to European-derived populations (He M et al, 2006). Among Asians; Mongolian and Chinese populations tend to be affected more, while variable prevalence is seen in Southeast Asia and India (He M et al, 2006). A meta-analysis of 29 published studies on Asian populations with PACG showed a strong association of prevalence with ethnic group through meta-regression analysis (β = 0.27, p = 0.009) (Cheng JW et al, 2014). However, there are minimal available data on race as a risk factor for progression of PACG. A study by Liza-Sharmini AT et al comparing Malay and Chinese ethnics in Malaysia reported that Malay patients presented with a more advanced disease and a higher tendency to progress within two years (Liza-Sharmini et al, 2014b).

Women are more at risk to develop PACG (Graham and Hollows, 1966; Lai JS et al, 2001; Vijaya L et al, 2006; Shen SY et al, 2008; Wang YX et al, 2010; Song WL et al, 2011; Liza-Sharmini AT et al, 2014a). Based on meta-analysis of 29 published studies on Asian populations, overall female to male ratio of PACG prevalence was 1.51:1 (95% CI, 1.01 to 2.28) (Cheng JW et al, 2014). However, there was no published data on the effect of gender on progression of PACG.

Higher incidence of PACG in women is mainly due to their ocular biometry (Chen HB et al, 1998; Wong TY et al, 2001; Congdon NG et al, 2002; George R et al, 2003; Wickremasinghe S et al, 2004; Ramani KK et al, 2007). PACG eyes are smaller in axial length (AL), have flatter corneas, shallower anterior chamber depth (ACD) and thicker lenses (Lowe RF, 1970; Alsbirk PH, 1976; Marchini G et al, 1998; Sihota R et al, 2008).

Eyes with shorter AL will tend to have thicker lenses sited more forward. Growth of the lens continues throughout life leading to increase in lens thickness and further anterior lens displacement which results to a shallowing of ACD (Lowe RF, 1970). Patient with PACG was found to have ACD that is 1.0 mm shallower than non-disease eyes, of which, 0.65 mm of shallowing attributed by the whole lens being anteriorly positioned and 0.35 mm by increased in lens thickness (Lowe RF, 1970).

A positive family history of PACG is an additional risk factor. The inheritance of PACG is believed to be polygenic (Lowe RF, 1972; Alsbrik PH, 1982; Wilensky JT et al, 1993), although both autosomal dominant and recessive inheritance pattern are seen in pedigrees with high prevalence of PACG. A study on Chinese population found that the disease prevalence among first-degree relatives of PACG patients, only parents account for an odd ratio of 8.76 (95% CI, 2.00 to 38.32) (Kong X et al, 2011). Characteristic-adjusted odds ratio of family history for PACG was 4.82 (95% CI, 2.08 to 11.19] and for severity of PACG was 1.61 (95% CI, 1.05 to 2.49) (Kong X et al, 2011).

It has also been observed that siblings of patients with angle closure have substantially higher risk of angle closure as compared to siblings of individual with open angles. The estimated odds of angle closure 21.1 times higher (95% CI, 2.8 to 160.1) among siblings of PACS, PAC or PACG (Venkatesh R et al, 2012). A high heritability of narrow angles of almost 60% was found (Amerasinghe N et al, 2011). Siblings of Chinese patients with PAC or PACG have almost a 50% probability of having narrow angles and are more than 7 times more likely to have narrow angles than the general population (Amerasinghe N et al, 2011).

PACG is a complex disease. Based on huge multiple population genetic study, rs11024102 in PLEKHA7; rs3753841 in COL11A1 and rs1015213 located between PCMTD1 and ST18 on Chromosome 8q were identified as potential genetic susceptibility markers (Visthana EN et al, 2012). Genetic marker was also identified that may associate with ocular biometry: anterior chamber depth; that increase the susceptible to ocular biometry changes to induce the development of PACG (Nongpiur ME et al, 2014). However, there is no susceptible genetic markers that may associate with the progression of PACG (Li et al, 2015).

IOP remains the only modifiable risk factor for development and progression of glaucoma. It is the basis of treatment for glaucoma. Mean IOP for PACG was found higher than POAG (Gazzard G et al, 2003; Lee YH et al, 2004). Fluctuation of IOP was higher in PACG compared to POAG (Gazzard G et al, 2003; Lee YH et al, 2004). Thus, it is perhaps the reason for acceleration of glaucomatous damage in PACG. The quest to identify other modifiable risk factor is still ongoing.

Hence, many hypothesis of modifiable risk factors have been proposed, these includes: physical activity (Williams PT, 2009), cigarette smoking (Williamson TH et al, 1995; Takashima Y et al, 2002; Kang JH et al, 2003; Lee AJ et al, 2003; Bonovas S et al, 2004; Edwards R et al, 2008; Wang D et al, 2012; Chiotoroiu SM et al, 2013; Jain V et al, 2016), body mass index (BMI) (Pasquale and Kang, 2009; Pasquale LR et al, 2010; Berdahl JP et al, 2012), mean arterial blood pressure (Bulpitt CJ et al, 1975; Klein BE et al, 2005; Xu L et al, 2007; Werne A et al, 2008), caffeine (Higginbotham EJ et al, 1989; Chandrasekaran S et al, 2005; Kang JH et al, 2008; Pasquale and Kang, 2009) and alcohol intake (Klein BE et al, 1993; Chiotoroiu SM et al, 2013).

It is interesting to note that all of these risk factors are strongly associated with our lifestyle, so perhaps by changing our way of life, the risks of developing and progression of glaucoma may be lowered. Therefore, an in-depth knowledge to these modifiable risk factors is of utmost importance to identify alternative measures that can be taken to prevent its onset and to sustain vision in diseased eyes in the presence of normal IOP. So far, the evidence of these proposed risk factors is still inconclusive. I won't be elaborating on the proposed modifiable risk factors raised above, but paying particular attention to cigarette smoking and physical activities which are the objective of this dissertation.

1.4.1   Cigarette smoking

Cigarette smoking is known to cause many diseases, such as cardiovascular disease, diabetes mellitus, lung disease and carcinoma (Solberg Y et al, 1998; Cheng ACK et al, 2000; Gallo V et al, 2009; Menvielle G et al, 2009). It is also associated with various ocular diseases such as age-related macular degeneration, cataract, and for the development and progression of thyroid eye disease (Solberg Y et al, 1998; Thornton J et al, 2005; Kelly SP et al, 2005; Thornton J et al, 2007; Lois N et al, 2008; Cong R et al, 2008). Studies on the effect of cigarette smoking on either intraocular pressure or glaucoma showed contradictory results (Wilson MR et al, 1987; Klein BE et al, 1993; Mansouri K et al, 2015).

1.4.1.1 Relationship between cigarette smoking and glaucoma

In 1976, a study conducted by Mehra et al reported following the last inhalation of a cigarette smoke, there was an acute rise in IOP that was statistically significant (Mehra KS et al, 1976). The Blue Mountains Eye Study observed a modest cross-sectional positive association between current smokers and IOP (Lee AJ et al, 2003). This was supported by another study which showed a higher mean IOP in smokers in relation to non-smokers (Afshan A et al, 2012). Numerous other studies have also found a positive association between smoking and increased IOP (Wu and Leske, 1997; Yoshida M et al, 2003; Yoshida M et al, 2014; Kamble G et al, 2016). The increase in IOP from has been supported by transcranial Doppler ultrasound studies which demonstrated faster ophthalmic artery blood flow after nicotine administration (Rojanapongpun and Drance, 1993).

In a case-control study, it was found that current cigarette smoking has a statistically significant associated with glaucoma with an odd ratio (OR) of 2.9 (95% CI, 1.3 to 6.6) (Wilson MR et al, 1987). A systematic review of 11 studies by Edwards et al (2008), which included 9 case-control studies, 1 cohort study, and 1 pooled analysis of 2 cohort studies, found little evidence of a compelling or consistent association between cigarette smoking and glaucoma. In 6 of the 9 case-control studies, ORs varied from 0.7 to 1.4 (Morgan and Drance 1975; Reynolds DC, 1977; Katz & Sommer, 1988; Charliat G et al, 1994; Stewart WC et al, 1994; Juronen E et al, 2000). Only the study by Fan BJ et al (2004) found a strong association between smoking and glaucoma, with an OR of 10.8 (95% CI; 1.9 to 63.0), the wide CI reflecting the small number of cases in the study, approximately 32 cases.

The Beaver Dam Eye Study did not find any association between cigarette smoking and prevalence of glaucoma (Klein BE et al, 1993). While in Iran, NilForooshan N et al (2008) also observed no association between cigarette smoking and glaucoma. In their case control study, smoking had an OR of 1.81 (95% CI; 0.74 to 4.41) towards developing glaucoma. This value however, was not statistically significant (p = 0.184).

1.4.1.2 Mechanisms of how cigarette smoking increases the risk of glaucoma

Various mechanisms have been postulated concerning the potential biologic association of cigarette smoking with glaucoma. In the mid-1970s, Mehra et al, in their research on effects of smoking on aqueous humor dynamics, noticed a rise of IOP of more than 5 mmHg after the last puff of a cigarette in 37.1% of primary glaucoma patients and only 11.4% in normal persons – a statistically significant difference. They proposed that cigarette smoking causes vasoconstriction which lead to a rise in episcleral venous pressure, thereby inhibiting aqueous outflow from the angle (Mehra KS et al, 1976).

Cigarette smoking has a strong effect on IOP in normotensive individual as demonstrated in a clinical study by Timothy and Nneli (2007). They found positive effect of smoking with systolic blood pressure readings (Timothy and Nneli, 2007). A number of studies have shown increase in IOP corresponds to the degree of arterial blood pressure (Sharrett AR et al, 1999; Wong TY et al, 2003; Smith W et al, 2004). Thus, smoking results in fluctuation and uncontrolled IOP which may lead to the progression of visual field defects to a more severe glaucoma.

Cardiovascular disease and its predictors, including diabetes mellitus, have been associated either with elevated IOP or with glaucomatous visual field loss (Klein and Klein, 1981; Klein BE et al, 1984), suggesting that cigarette smoking, with its known effects on vascular disease, must be considered. The levels of plasma fibrinogen are known to rise with age (Hume R, 1961; Moser and Hajjar, 1966). Chronic smoking may induce hyperfibrinogenaemia, as apparent by the accentuation of this rise in cigarette smokers (Ogston D et al, 1970). Bearing in mind the effect of smoking in producing oxidative stress and damage to the small vessels (Jensen JA et al, 1991), smoking may be indicted in the aggravation of factors related to glaucoma.

It has been reported that arterial blood flow to the optic nerve head are compromised in smokers (Williamson TH et al, 1995; Kaiser HJ et al, 1997). Cigarette smoking plays a part in the development of vascular disease by causing occlusion of the arterial lumina from atherosclerosis and intimal thickening. Free-radical-mediated oxidative stress in cigarette smoking play a pivotal role in the development of atherosclerosis (Gibbons and Dzau, 1994; Kojda and Harrison, 1999; Nedeljkovic ZS et al. 2003). The vascular dysfunction caused by smoking is initiated by reduced nitric oxide (NO) bioavailability and further aggravated by the increased expression of adhesion molecules and subsequent endothelial dysfunction (Kojda and Harrison, 1999; Messner and Bernhard, 2014). Increased adherence of platelets and macrophages provokes the development of a pro-coagulant and this induces an inflammatory environment (Messner and Bernhard, 2014). Subsequent to trans-endothelial migration and activation, macrophages consume oxidized lipoproteins arising from oxidation modifications and differentiate into foam cells (Messner and Bernhard, 2014). Furthermore to direct physical damage to endothelial cells, smoking induces tissue remodelling, and prothrombotic processes

together with activation of systemic inflammatory signals, all of which contribute to atherogenic vessel wall changes (Messner and Bernhard, 2014). Inadequate blood flow reduces vascular supply of nutrient and oxygen to optic nerve head causing glaucomatous neuropathy.

The precise toxic components of cigarette smoking and the mechanism involved in the development of ocular diseases is not clearly understood. The high concentration of free radicals in particulate (tar) and gas phases are believed to play an important role (Ambrose and Barua, 2004). This oxidative stress damages the ocular tissues, particularly, the ganglion cells in optic nerve head leading to an acceleration of glaucomatous damage (Tezel G, 2006; Nita M and Grzybowski A, 2016). In addition to the direct effect of free radicals from the cigarette smoke, it can also result in the activation of endogenous source of free radicals, such as nitric oxide synthase (NOS), xanthine oxidase, and nicotinide adenine dinucleotide phosphate (NADPH) oxidase, etc. Hence, smoking leads to increase in oxidative stress, reduction in NO generation and bioavailability, and activation of inflammatory process resulting in the initiation and progression of tissue damage (Ambrose and Barua, 2004).

1.4.1.3   Smoking status

A meta-analysis of several epidemiological studies on smoking observed a higher risk of developing glaucoma for current smokers as compared to ex-smokers (Bonovas S et al, 2004). A pooled OR for the risk of glaucoma seen with current smoking was 1.37 (95% CI, 1.00 to 1.87) from a meta-analysis comprising of 3 cross-sectional studies and 3 case-control studies (Bonovas S et al, 2004). In contrast, meta-analysis from 2 cross-