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

DR TAN KOK LEONG

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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.

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Dr. Tan Kok Leong

P-UM0019/12

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ABSTRAK

PENGENALAN

Glaukoma sudut terbuka primer (GSTP) ialah jenis glaukoma yang paling sering terjadi. Pengetahuan tentang penyakit ini di kalangan populasi Melayu amat terbatas. Berdasarkan bukti kajian sekarang, tekanan intraokular merupakan satu-satunya faktor risiko yang boleh diubah dalam menentukan keterukan penyakit GSTP. Pengaruh faktor gaya hidup seperti merokok and aktiviti fisikal ke atas tahap keterukan GSTP masih belum dapat dikenalpastikan dengan jelas.

OBJEKTIF

Tujuan kajian ini adalah untuk menentukan hubungkait antara merokok dan aktiviti fisikal dengan tahap keterukan GSTP di kalangan pesakit Melayu di Malaysia.

METODOLOGI

Satu kajian keratan rentas yang melibatkan pesakit GSTP Melayu telah dilaksanakan dari November 2014 sehingga Disember 2016. Status merokok didokumenkan dengan menggunakan soal selidik dalam bahasa Melayu daripada *Singapore Malay Eye Studies* (SiMES) yang telah divalidasikan, dan pernah digunakan di kalangan pesakit glaukoma. Penilaian aktiviti fisikal dilakukan dengan menggunakan *International Physical Activity Questionnaire* (IPAQ) versi bahasa Melayu yang telah divalidasikan. Ujian medan penglihatan Humphrey 24-2 juga dilakukan. Tahap keterukan GSTP ditentukan berdasarkan sistem skor *Advanced Glaucoma Intervention Study* (AGIS) yang telah dimodifikasi, dengan menggunakan hasil dua ujian medan penglihatan yang dilakukan secara berturut-turut dan mempunyai indeks ketepatan yang baik. Proses skoring ini dilakukan oleh dua orang penyelidik. Tahap

keterukan GSTP diketegorikan ke peringkat ringan (skor 0-5), sederhana (skor 6-11) dan serius (skor 11-20). Analisis univariat telah digunakan untuk menentukan faktor risiko lain yang mungkin ada hubungan dengan GSTP. Hubungan antara merokok dan aktiviti fisikal dengan tahap keterukan GSTP dianalisis dengan menggunakan regressi linear pelbagai. Pembolehubah pengeliru seperti usia, jantina, tahap pendidikan dan ko-morbid sistemik turut dipertimbangkan dalam analisis.

KEPUTUSAN

Kajian ini melibatkan 150 orang pesakit GSTP berbangsa Melayu, yang terdiri daripda 101 orang lelaki dan 49 orang perempuan. Kajian ini tidak menunjukkan hubungkait yang signifikan antara aktiviti fisikal dengan skor AGIS pesakit GSTP. Terdapat korelasi yang signifikan antara status merokok dengan skor AGIS di kalangan pesakit GSTP ($r = 0.175$, $p = 0.032$). Akan tetapi, tempoh merokok tidak didapati mempunyai korelasi dengan skor AGIS ($r = 0.142$, $p = 0.083$). Umur pesakit GSTP menunjukkan hubungan linear positif dengan skor AGIS.

KESIMPULAN

Merokok mungkin merupakan suatu faktor risiko bolehubah di kalangan GSTP Melayu. Kajian ini menemukan hubungan yang signifikan antara status merokok dengan tahap keterukan GSTP. Walau bagaimanapun, kajian yang lebih lanjut diperlukan untuk menentukan kuantiti pengaruh merokok ke atas tahap keterukan GSTP. Pesakit GSTP perlu dinasihati supaya menjauhi rokok, memandangkan merokok boleh menyebabkan GSTP menjadi semakin teruk. Tiada hubungan signifikan ditemui antara aktiviti fisikal dengan tahap keterukan GSTP di kalangan orang Melayu. Keterbatasan kajian keratan rentas dan IPAQ mungkin tidak menampilkan pengaruh sebenar aktiviti fisikal ke atas tahap keterukan GSTP.

ABSTRACT

INTRODUCTION

Primary open angle glaucoma (POAG) is the most common type of glaucoma. Data regarding this disease among Malay population is scarce. Currently, intraocular pressure is the only modifiable risk factor of POAG that was consistent among past studies. Influence of lifestyle factors such as cigarette smoking and physical activity on the severity of POAG is still inconclusive.

OBJECTIVE

The aim of this study is to determine the association of cigarette smoking and physical activity with the severity of POAG among Malay patients in Malaysia.

METHODOLOGY

A cross sectional study involving Malay POAG patients was conducted between November 2014 and December 2016. The smoking status was documented using a validated Malay language questionnaire adopted from Singapore Malay Eye Studies (SiMES), which also has been used among glaucoma patients. The physical activity assessment was carried out using the validated Malay version of International Physical Activity Questionnaire (IPAQ). Humphrey visual field (HVF) 24-2 test was conducted. POAG severity was determined according to modified Advanced Glaucoma Intervention Study (AGIS) scoring system, based on two consecutive reliable HVF, by two masked investigators. Severity of POAG was catogerized into mild (score of 0 to 5), moderate (score of 6 to11) and severe (score of 11 to 20). Univariate analysis was done to evaluate risk factors associated with POAG. The

association of cigarette smoking, and physical activity level with AGIS score was analyzed using multiple linear regression. Confounders such as age, gender, education status, and systemic co-morbidities were considered in the analysis.

RESULTS

A total of 150 Malay patients with POAG were recruited; comprising of 101 males and 49 females. This study did not find any significant association between physical activity and the AGIS score of Malay POAG patients. There was a significant correlation between cigarette smoking status and the AGIS score ($r = 0.175$, $p = 0.032$) among Malay POAG patients. However, the duration of smoking was not found to be significantly correlated with the AGIS score ($r = 0.142$, $p = 0.083$). There was a positive linear relationship between age of POAG patient and AGIS score.

CONCLUSION

Cigarette smoking is a potential modifiable risk factor for POAG among Malays. This study found significant association of smoking status with POAG severity. However further study is needed to quantify the influence of smoking on POAG severity. POAG patient should be advised and properly educated to refrain from cigarette smoking, as smoking could to lead to more severe POAG and progression of the disease. There was no significant association between physical activity and severity of POAG in Malays. Limitation of cross sectional study and IPAQ may not reflect the actual influence of physical activity on the severity of POAG.

CHAPTER 1
INTRODUCTION

1.1 Glaucoma

Glaucoma is a progressive optic neuropathy involving characteristic structural damage to the optic nerve and characteristic visual field defects (Gupta and Weinreb, 1997). Glaucoma can be classified into primary, secondary, and developmental glaucoma. Primary glaucoma is categorised as glaucoma without any association with ocular or systemic disorders. The morphology of angle structure differentiates primary open angle glaucoma (POAG) from primary angle closure glaucoma (PACG) (Kroese and Burton, 2003).

Despite of progress in the understanding of glaucoma, the definition of glaucoma remains elusive. Currently, the most acceptable diagnosis of glaucoma is based on the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) glaucoma case definition and classification system (Foster, et al., 2002). The diagnosis of glaucoma can be made according to three levels of evidence. The highest level of certainty requires structural and functional evidence. It involves eyes with a cup : disc ratio (CDR) or CDR asymmetry more than 97.5th percentile for the normal population, or a neuroretinal rim width reduced to less than 0.1 CDR (between 11 to 1 o'clock or 5 to 7 o'clock) that also showed a definite visual field defect consistent with glaucoma. The second category of diagnosis is used in subjects with advanced structural damage but unproved field loss. If the subject could not satisfactorily complete visual field testing but had a CDR or CDR asymmetry more than 99.5th percentile for the normal population, glaucoma will be diagnosed solely on the structural evidence. In diagnosing category 1 or 2 glaucoma, there should be no alternative explanation for CDR findings (e.g. dysplastic disc or marked anisometropia) or the visual field defect (e.g. retinal vascular disease,

macular degeneration, or cerebrovascular disease). Category 3 diagnosis involves those with optic disc not seen and field test impossible. If it is not possible to examine the optic disc, glaucoma is diagnosed if the visual acuity is worse than 3/60 and the IOP >99.5th percentile, or the visual acuity worse than 3/60 with evidence of glaucoma filtering surgery (Foster, et al., 2002).

1.2 Primary Open Angle Glaucoma

As mentioned in previous section, glaucoma is to be diagnosed according to the highest level of evidence, requiring optic disc abnormalities (vertical cup: disc ratio, VCDR > 97.5th percentile in the normal population) and visual field defect consistent with glaucoma. POAG is defined as optic nerve damage meeting the category of evidence above, in an eye which does not have evidence of angle closure on gonioscopy, and where there is no identifiable secondary cause (Foster, et al., 2002).

In order to differentiate POAG from other types of glaucoma, congenital forms of glaucoma and secondary causes of glaucoma have to be excluded (Wolfs, et al., 2000). Secondary causes of open angle glaucoma (OAG) whether at pre-trabecular, trabecular or post trabecular sites have to be excluded (Bowling, 2016). Pre-trabecular causes of OAG include fibrovascular tissue, epithelial ingrowth, and iridocorneal endothelial syndrome; trabecular causes include obstruction of trabecular meshwork by pseudoexfoliative material, red blood cell or protein; and post trabecular causes that elevate episcleral pressure such as carotid-cavernous fistula.

1.2.1 Epidemiology of Primary Open Angle Glaucoma

It was estimated that around 60 million people have glaucoma in 2010 (Quigley and Broman, 2006). 74% of these people have OAG. POAG is the most common type of glaucoma. It was also estimated that 4.5 million people will be bilaterally blind from OAG in 2010 and increased further to 5.9 million in 2020. Alarmingly, half of world bilateral blindness is in Asian (Wong, Loon and Saw, 2006). This is due to increase life span in Asia. Asians have been reported as having a high prevalence of glaucoma (Wadhwa and Higginbotham, 2005). The term Asians includes individuals from the Far East, Southeast Asia, and the Indian subcontinent. In general, the prevalence of glaucoma in Asian populations range from 2.4% to 5% (Foster, et al., 2000; Ramakrishnan, et al., 2003; Rahman, et al., 2004; He, et al., 2006; Shen, et al., 2008).

Mean prevalence for OAG worldwide in 2010 was 1.96% (Quigley and Broman, 2006). POAG had the highest prevalence among African descents (Quigley and Broman, 2006; Tham, et al., 2014). In Latin American and Chinese regions, prevalence of OAG in the oldest age groups was almost similar to that of Africans. Prevalence of OAG in India, Europe, and Japan was lower and similar among them (Quigley and Broman, 2006). Urban areas also had higher prevalence of POAG than rural areas (Tham, et al., 2014).

1.2.2 Prevalence of Primary Open Angle Glaucoma in Malay populations

In the 2010 census, the population of Malaysia was 28.3 million, making it the 42nd most populated country in the world. Malaysia was comprised of 67.4% Malays and *Bumiputera*, 24.6% Chinese, 7.3% Indian and 0.7% other ethnic groups

(Department of Statistics Malaysia, 2010). According to the National Eye Survey (NES) 1996, glaucoma ranked fifth in the cause of bilateral blindness in Malaysia (1.77%) (Zainal, et al., 2002). The NES was carried out in the respondents' houses, and did not include refraction, slit lamp or visual field examinations. Underestimation of the prevalence of glaucoma in Malaysia was likely in NES. The overall response rate was just 69%. To date, there is no accurate data on the prevalence of glaucoma in Malaysia (Ministry of Health Malaysia, 2008).

Malays is the third largest ethnic group in Asia, accounting for 5% of the world population. Around 300 to 400 million Malays are living in Malay Archipelago of South-East Asia. However, there is limited study on glaucoma among Malays (Foong, et al., 2007). Singapore Malay Eye Study (SiMES) is the only well conducted population based study on urban Malays residing in Singapore. Based on SiMES, the prevalence of glaucoma in an urban Malay population was 3.4%, with POAG contributing 2.5% and PACG only 0.12% (Shen, et al., 2008). This emphasizes the importance of POAG in Malays. Thus the understanding of glaucoma in Malays is important as part of the global prevention of blindness strategy.

1.3 Severity and progression of glaucoma

1.3.1 Severity and progression of Primary Open Angle Glaucoma

POAG is a slow and progressive disease that requires lifelong monitoring (Brusini and Johnson, 2007). A standardized staging of severity of glaucomatous visual field damage would be very useful in deciding treatment strategy and long term follow-up. Various staging systems have been proposed. Some are based on the number of depressed points, either in the total or pattern deviation printout of

automated perimetry; while others utilize visual field indices (Brusini and Johnson, 2007). For example, the Advanced Glaucoma Intervention Study (AGIS) visual field defect score is based on both the number and depth of adjacent depressed test points in the nasal field, upper and lower hemifield (AGIS, 1994).

Data regarding the natural history of visual field progression in glaucoma are very limited, as treatment is normally started once glaucoma is diagnosed (Rossetti, et al., 2010). Although the mean overall progression rate for OAG was -1.08 dB per year, the progression rate for high-tension glaucoma and normal-tension glaucoma were -1.31dB and -0.36 dB respectively. Progression of visual field defect was faster in older patients than younger patients (Heijl, et al., 2009).

Despite treatment, most of the POAG patients would experience progressive visual field loss (Zahari, et al., 2006). Progressive visual field loss in POAG was associated with the patient's baseline glaucoma status. POAG patients with more depressed initial visual field were more likely to show progression. As there is no gold standard for evaluating progression of visual field loss in POAG and results from the various methods might be different, more than one method could be applied to ascertain the presence of any progression (Zahari, et al., 2006).

1.3.2 Evaluation of glaucoma progression

The importance of glaucoma progression evaluation and its influence in the management decision is well recognized (Rossetti, et al., 2010). Glaucoma progression could be evaluated in terms of visual field and structural changes.

1.3.2.1 Visual field changes

Several algorithms have been used to identify glaucomatous visual field progression using various approaches to differentiate true change from test–retest variability. Two commonly used methods are event- and trend based approaches (Medeiros, et al., 2012a; Rao, et al., 2013).

1.3.2.1.1 Event analysis

In event-based approach, visual field progression is determined by comparing the visual field sensitivities of current examinations with previously established baseline tests. Visual field progression is said to be present if a predefined threshold in the VF parameter is exceeded in a specific number of test locations (Medeiros, et al., 2012a; Rao, et al., 2013). The thresholds are based on test–retest variability levels obtained from patients followed up over relatively short periods during which it is reasonable to assume the disease has not progressed (Medeiros, et al., 2012a). This method is used by the Guided Progression Analysis (GPA) software available in Humphrey Field Analyzer (Medeiros, et al., 2012a; Rao, et al., 2013).

1.3.2.1.2 Trend analysis

Trend based analysis shows the rate of change of visual field parameters (Rao, et al., 2013). In trend-based approach, visual field tests available during the course of follow-up are analyzed for the presence of statistically significant change over time, normally using a linear regression method (Medeiros, et al., 2012a). Humphrey Field Analyzer software provides a trend-based progression analysis based on linear regression of the visual field index (VFI). VFI is the aggregate

percentage of visual function for each point of a visual field where the visual thresholds are estimated (Rao, et al., 2013). If global trend analyses are used, increasing the frequency of visual field test would enable earlier detection of glaucoma progression (Nouri-Mahdavi, Zarei and Caprioli, 2011).

1.3.2.2 Structural changes

An accurate structural evaluation of optic nerve head and retinal nerve fiber layers could be done using advanced and expensive technology (Brusini and Johnson, 2007). Sophisticated machine such as spectral-domain optical coherence tomography (SDOCT) could be utilized to detect progression of structural damage as evidence by neuronal damage in glaucoma. However, severity of the disease has to be taken into consideration when using such method. When using SDOCT, average retinal nerve fiber layer thickness showed a linear relationship with retinal ganglion cell counts throughout most of the spectrum of glaucoma severity, but reaching a plateau in advanced disease (Medeiros, et al., 2012b).

1.4 Factors affecting severity and progression of Primary Open Angle Glaucoma

1.4.1 Non-modifiable risk factors

1.4.1.1 Age

Age was identified as an important risk factor for POAG (Seddon, Schwartz and Flowerdew, 1983; David, et al., 1987; Klein, et al., 2006). Change in cupping (CDR) in relation to IOP is especially apparent in those 75 years of age or older. These persons may benefit in regard to risk of glaucoma from surveillance of IOP. Both incidence and prevalence increase more than linearly with age. Age maybe

related to the deterioration of relevant tissues with time, potentiating ganglion cell death. Older age is also a measure of the length of time that the person is exposed to other risk factors before developing disease. Age may also be a measure of duration of POAG. Longer duration of POAG is expected to be associated with greater damage when the disease is progressive. Older age might also modify the attitude of the patient toward disease, possibly reducing compliant to treatment (Boland and Quigley, 2007).

1.4.1.2 Ethnicity

African-Caribbean ethnic has higher prevalence of POAG, with younger onset and higher severity (Wilson, et al., 1985; Tielsch, et al., 1991). Progression of POAG as evidenced by further structural optic disc damage and visual field loss was more significant in the eyes of blacks (Wilson, et al., 1985). This could indicate an underlying genetic susceptibility to POAG (Tielsch, et al., 1991). Prevalence of OAG among Indian, European, and Japanese were lower (Quigley and Broman, 2006).

1.4.1.3 Refractive status

The Blue Mountains Eye Study reported a strong relationship between myopia and OAG. The study showed that OAG was present in 4.2% of eyes with low myopia, and 4.4% of eyes with moderate-to-high myopia compared to 1.5% of eyes without myopia (Mitchell, et al., 1999). The Beijing Eye Study also reported marked to high myopia with refractive error exceeding -6 D could be a risk factor associated with glaucoma. The prevalence of glaucoma did not vary significantly between the hyperopic and the emmetropic subjects, or the subjects with low myopia (Xu, et al.,

2007). Axial length and myopia were also reported to be related to progressive visual field damage in POAG (Perdicchi, et. al., 2007).

1.4.1.4 Optic disc characteristics

Optic disc characteristics that predict the development or progression of glaucomatous visual field defects in POAG include small neuroretinal rim and large beta zone of parapapillary atrophy (Girkin, et al., 2003; Jonas, et al., 2004). This influence was more marked in eyes with more advanced stage of POAG. However, the size of the optic disc and α-zone of parapapillary atrophy did not seem to influence the progression of glaucomatous optic nerve head changes (Jonas, et al., 2004). Pre-existing cup-disc-ratio of more than 0.7 is found to be associated with higher risk of OAG (Leske, et. al., 2001; Le, et al., 2003).

1.4.1.5 Gender

Gender is also a factor influencing the progression of POAG. It was reported that female sex was a predictor of progression, with female twice likely to progress compared to male (Chauhan, et al., 2008). The Collaborative Normal-Tension Glaucoma Study Group also reported similar finding (Drance, et al., 2001). However female gender was not found to be a predictor of glaucoma progression in Early Manifest Glaucoma Trial (Heijl, et al., 2002). This discrepancy was postulated to be due to genetic and environmental differences between the populations, as well as sample selections and study methodology (Chauhan, et al., 2008).

1.4.2 Modifiable risk factors

1.4.2.1 Intraocular pressure (IOP)

In the past, although studies have identified several risk factors for POAG, most are non-modifiable. Previously the only modifiable risk factor that was consistent among different studies is intraocular pressure (IOP) and has been extensively studied (Lee, et al., 2003; Coleman and Miglior, 2008). Higher IOP at baseline was reported to be a risk factor for glaucoma progression in the Early Manifest Glaucoma Trial (Leske, et al., 2007). Canadian Glaucoma Study also had found that IOP was a powerful predictor of visual field progression, with 19% increase of risk for every 1 mmHg raised in IOP (Chauhan, et al., 2008). Target IOP needs to be individualized for each patients and lower target IOP should be used if there is evidence of significant progression (Rossetti, et al., 2010).

. 1.4.2.2 Cigarette smoking

Smoking is postulated to affect IOP and indirectly on the progression of POAG. Timothy and Nneli (2007) had showed that smoking had a significant effect on IOP and blood pressure. Elevation of IOP and arterial blood pressure was believed due to hypersecretory role of nicotine, the principal constituent of cigarette (Timothy and Nneli, 2007). Cigarette smoke also has atherosclerotic and thrombotic effects on the ocular capillaries. Smoking enhances the generation of free radicals and decreases the levels of antioxidants in the blood circulation, aqueous humour, and ocular tissue. All these will potentiate ganglion cell death, possibly worsen the glaucoma (Cheng, et al., 2000). Mehra, Roy and Khare (1976) reported an acute rise in IOP within 5 minutes of the last puff on a cigarette in 11.4% of normal subjects

and 37.1 % of patients with primary glaucoma. Pre-puff IOP was restored within 15 to 30 minutes. In the long run perhaps the recurrent elevation of IOP secondary to chronic smoking indirectly will lead to the progression of POAG. However, thus so far, the available studies could not conclude an association of smoking with POAG nor IOP due to conflicting results (Shephard, et al., 1978; Wilson, et al., 1987; Klein, Klein and Ritter, 1993; Lee, et al., 2003; Ramdas, et al., 2011). Wilson et al. (1987) found a positive association of smoking with POAG through a case-control study. Contradictory finding was found in the Beaver Dam Eye Study (Klein, Klein and Ritter, 1993). On the other hand, the Blue Mountains Eye Study reported a modest cross-sectional positive association for current smokers and IOP (Lee, et al., 2003). On contrary the Rotterdam Study and Los Angeles Latino Eye Study could not find an association between smoking and OAG (Doshi, et al., 2008; Ramdas, et al., 2011). Kang, et al. (2003a) also reported that smoking did not increase the risk of POAG. Thus the influence of smoking on POAG is still inconclusive. Conflicting results from different studies of the effect of smoking on IOP have not established a causal relationship between the two (Cheng, et al., 2000).

The definitions used for smoking status might be dissimilar in different surveys (Australian Bureau of Statistics, 2005; Beland, 2005; Goddard, 2006; Centers for Disease Control and Prevention, 2007; Ministry of Health New Zealand, 2008; Institute for Public Health Malaysia, 2015). The key point of difference is whether the definition of current smoker includes both daily and non-daily smokers, or daily smokers only (Ministry of Health New Zealand, 2008; Institute for Public Health Malaysia, 2015). Apart from the difficulty in the definition of smoker, there is also difficulty in quantifying environmental tobacco smoke. It is not easy to estimate

the amount of environmental smoke contributed by a neighbour, housemate or stranger on the street who smokes (World Health Organization, 2001; Ramdas, et al., 2011).

1.4.2.3 Physical activity

Physical activity or exercise has long been known to reduce risk of many diseases. However the effect of exercise on POAG severity is still not yet well established. Exercise can be categorized into dynamic or isometric. Dynamic exercise is defined as work performed by a muscle while changing the length of that muscle (Risner, et al., 2009). In practice, this is achieved by walking, running, or cycling for a period of time. Janiszewska-Zygier (1963) reported dynamic exercise's ability to decrease IOP. Several studies have also demonstrated similar effect of exercise on IOP (Leighton and Phillips, 1970; Myers, 1974; Pasquale and Kang, 2009). All these studies noted IOP is lower in the immediate post exercise period (typically in the minutes) compared with values taken before exercise. The exact effect of exercise on the severity of POAG is yet to be ascertained.

Isometric exercise is defined as work performed by a muscle while maintaining constant muscle length (Risner, et al., 2009). In practice, this can be achieved by assuming a squat position or forcefully clinching ones fist for a period of time. Like dynamic exercise, isometric exercise has been documented to lower IOP in the acute post exercise period (Harris, et al., 1992). Marcus, et al. (1974) also showed a decrease in IOP following isometric. Isometric exercise is postulated to cause hyperventilation and hypocapnia, which correlates with the decrease in IOP. However the mechanism on how hypocapnia decreases IOP is not clear. Maximal

isometric exercise like weight lifting will result in increased intracranial pressure, similar to Valsalva, causing an increase in IOP (Vieira, et al., 2006; Pasquale and Kang, 2009). To the best of our knowledge, to date there is still no available study linking exercise with the severity of POAG.

1.4.2.4 Dietary intake

Consumption of caffeine, a major constituent of coffee may cause elevation of IOP (Ajayi and Ukwade, 2001). A cup of coffee, the primary dietary source of caffeine, causes a 1 to 4 mmHg rise in IOP that lasts for at least 90 minutes (Pasquale and Kang, 2009). Caffeine has been shown to be a risk factor in the development of POAG, but only in subjects with a family history of glaucoma (Brown, 2010). The association of caffeine with the severity of POAG is still under investigation.

In the vascular theory of glaucoma, it has been hypothesized inflammation, arteriosclerosis or thrombosis of blood vessel lead to vascular dysregulation (Flammer and Mozaffarieh, 2007) and may disrupt auto regulation of ocular blood flow, resulting in ischemic optic nerve damage and glaucomatous optic neuropathy (Amerasinghe, et al., 2008a). Sedentary lifestyles, combined with high consumption of cholesterol or lipid with minimal physical activity, may contribute to higher incidence of arteriosclerosis or thrombosis. Thus, theoretically, this may also affect the severity and progression of POAG.

Daily caloric consumption may also play a role in the progression and severity of POAG. High calorie intake with relatively sedentary lifestyle contributes to higher body mass index (BMI). The relationships between BMI and POAG, and

BMI and IOP seem to be contradictory. The Beaver Dam Eye Study (Klein, Klein and Linton, 1992), the Tajimi Study (Kawase, et al., 2008) and Rotterdam Study (Ramdas, et al., 2011) found a positive association between BMI and IOP. On the other hand, the Barbados Eye Study (Wu and Leske, 1997) and the Singapore Malay Eye Study (Amerasinghe, et al., 2008b) reported an inverse relation of BMI to POAG, suggesting a protective effect of BMI on POAG. A possible mechanism explaining the inverse association of BMI with IOP could be an increased orbital pressure because of excess fat tissue, with a rise in episcleral venous pressure and a consequent increase in IOP (Ramdas, et al., 2011). Obesity may lead to an increase in the viscosity of blood, with a consequent reduction in outflow resistance of the episcleral veins (Shiose, 1990; Kawase, et al., 2008).

Measuring IOP using Goldmann applanation tonometry involves patient pushing forward thorax and abdomen while holding breath. This acts like a Valsalva maneuver and is especially relevant for those who are obese. Therefore, measurement of IOP with Goldmann applanation tonometry in those with a high BMI might lead to an overestimation of the actual IOP and as a consequence might contribute to the contradictory relationships between BMI and IOP, and BMI and POAG. The higher IOP with a high BMI should have resulted in an expected higher incidence of POAG. However, this effect was not observed and a multivariate analysis yielded a protective effect of BMI on POAG incidence (Ramdas, et al., 2011). It is still unclear whether higher BMI may increase or decrease the likelihood of having glaucoma and what confounding factors associated with BMI that may play a role (Coleman and Kodjebacheva, 2009).

Sodium intake might influence the severity and progression of POAG. Difference in dietary content of sodium can lead to changes of systemic blood pressure which influences the IOP. Systemic hypertension (Wong and Mitchell, 2007) and hypotension (Graham, et al., 1995) have both been reported as potential risk factors in glaucoma. It has been suggested that chronic hypertension may cause microvascular damage, whereas hypotension may reduce local perfusion. Both mechanisms might cause further glaucomatous progression in the face of IOP elevation or poor vascular autoregulation of blood flow (Werne, et al., 2008).

Antioxidant is food with anti-oxidative properties. Examples are carotenoids (α-carotene, β-carotene, lutein, zeaxanthin, β-cryptoxanthin, and lycopene), vitamins (retinol equivalents, B1, B6, B12, E and C) and flavonoids (Ramdas, et al., 2012). Reduced antioxidant intake in daily diet of subjects might contribute to the severity of POAG in view reactive oxygen species are related to the pathogenesis POAG (Coleman and Kodjebacheva, 2009). Oxidative DNA damage in the ocular epithelium that regulates the trabecular meshwork is more severe in glaucoma patients compared to controls (Sacca, et al., 2005). Theoretically, oxidative stress is related to the neuronal cell death affecting the optic nerve (Izzotti, et al., 2003). Two studies (Kang, et al., 2003b; Coleman, et al., 2008) also suggested a relationship existed between the greater intake of Vitamins B2 and A, obtained from natural food sources, and the decreased likelihood of glaucoma.

1.5 Rationale of the study

The Malay race comprises the majority of Malaysia population. Malays constituted 63.1% of the population in Peninsular Malaysia (Department of Statistics

Malaysia, 2010). However knowledge about eye disease in Malay population is relatively scarce. Most knowledge about ocular disease has been derived from Caucasian, Chinese, or Japanese studies. Singapore Malay Eye Study (SiMES) is the only well conducted population based eye study on Malays. It would be of value to conduct a study involving Malay population in Malaysia to determine risk factors involved in eye disease like glaucoma. Data from this study will serve as nominal data for better understanding of progression and severity of glaucoma among Malays who are the majority ethnic group in Malaysia.

POAG is a chronic disease requiring life-long follow-up. In the public hospitals, the cost of treating POAG patients consumes a significant proportion of health care budget, ranging from 70% to 80% of total drug expenditure allocated to ophthalmology departments in the Ministry of Health Malaysia (Ministry of Health Malaysia, 2008). Lifestyle modification is inexpensive compared to burden of treatment. Moreover the knowledge of modifiable lifestyle factors affecting the risk for POAG may provide great contribution for possible primary prevention of POAG, especially for those with known demographic or genetic risk factors. Primary preventive measures through lifestyle modification may also reduce the burden of visual disability caused by POAG, which is projected to be considerable by the year 2020 (Pasquale and Kang, 2009).

Until now, IOP is the only modifiable risk and prognostic factor identified for POAG. It is important to identify other modifiable risk factors to aid in halting the progression of POAG severity (Coleman and Miglior, 2008). In addition, there are minimal population studies on lifestyles as risk factor for glaucoma with

inconclusive findings (Doshi, et al., 2008; Pasquale and Kang, 2009; Ramdas, et al., 2011; Wise, et al., 2011; Renard, et al., 2013). If certain lifestyle factors could be shown to be consistently associated with the severity of POAG, those factors could be targeted for better management of POAG in general.

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