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

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ABSTRAK

PENGENALAN

Glaukoma sudut terbuka primer merupakan jenis glaukoma yang paling lazim. 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 dan tahap keterukan penyakit glaukoma sudut terbuka primer di kalangan pesakit berbangsa Cina di Malaysia.

KAEDAH KAJIAN

Satu kajian rentas telah dijalankan yang melibatkan pesakit glaukoma sudut terbuka primer di antara November 2014 dan Mac 2016 di klinik mata, Hospital Kuala Lumpur dan Hospital Universiti Sains Malaysia. Hanya pesakit glaukoma yang berbangsa Cina dan dapat melakukan ujian medan penglihatan menggunakan analisis Humphrey visual field 24-2 yang tepat secara berulang sekurang-kurangnya dua kali, telah dipilih. Tahap

keterukkan 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 terbuka. 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 terbuka primer (103 orang pesakit lelaki dan 47 orang pesakit perempuan) terlibat dalam kajian ini. Terdapat hubung kait yang signifikan di antara amalan merokok dan tahap keterukkan penyakit glaucoma

($p<0.001$). Merokok meningkatkan skor AGIS sebanyak 3.3 (ubahan b 3.26, 95% CI 1.67, 4.86). Setiap batang rokok yang dihisap menyebabkan peningkatan skor AGIS sebanyak 0.5 (ubahan b 0.50, 95% CI 0.05, 0.86). Tetapi tempoh merokok (dalam kiraan tahun) serta tempoh berhenti daripada merokok (dalam kiraan tahun) tidak menunjukkan hubung kait yang signifikan sama ada dengan tahap keterukkan penyakit glaukoma atau skor AGIS.

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 4.4 (ubahan b -4.39, 95% CI -5.53,-3.24). Bagi setiap sehari peningkatan aktiviti fisikal dalam seminggu akan menurunakan skor AGIS sebanyak 0.2 (95% CI -0.23, -0.15). Terdapat juga hubung kait linear yang signifikan di antara BMI dan skor AGIS (ubahan b 0.33, 95% CI 0.11, 0.56, $p<0.001$).

KESIMPULAN

Amalan merokok dan aktiviti fisikal merupakan faktor risiko boleh ubah bagi tahap keterukan penyakit glaukoma sudut terbuka 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

Primary open angle glaucoma (POAG) is the most common type of glaucoma. Progression of glaucoma is common; despite good control of intraocular pressure (IOP). Factors associated with progression of glaucoma can be divided into non-modifiable and modifiable risk factors. There is limited research on identification of modifiable risk factors. Modifiable risk factor include cigarette smoking and physical activity. There are evidences on the potential association between current cigarette smoking and physical activities on the development of POAG. However, there is no available evidence on the potential association between cigarette smoking and physical activities and severity of POAG.

OBJECTIVE

To determine the association between cigarette smoking and physical activity on the severity of primary open angle glaucoma (POAG) in Malaysian Chinese patients.

METHODOLOGY

A cross-sectional study was conducted between November 2014 and March 2016 in eye clinic of Hospital Kuala Lumpur and Hospital Universiti Sains Malaysia. Only patients who were able to provide two consecutive reliable and reproducible Humphrey

visual field 24-2 analyses were included. Severity of glaucoma was based on modified AGIS scoring system on HVF and divided 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 questionnaire 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 cigarette per day was also documented. Physical activity status was assessed based on validated Bahasa Malaysia version of International Physical Activity Questionnaire (IPAQ). Based on their physical acticities over 7 days, POAG patients were divided 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 Chinese patients were recruited (103 male and 47 female). There was significant association between cigarette smoking and severity of glaucoma ($p < 0.001$). Smoking increases the AGIS score by 3.3 (adjusted b 3.26, 95% CI 1.67, 4.86, $p < 0.001$). However, there was no significant association in duration of smoking (in years) and duration since stopped smoking (in years) with severity of glaucoma.

There was significant inverse relationship between physical activity and AGIS score. Every increase in physical activity reduces the AGIS score by 4.39 (adjusted b -4.39,

95% CI -5.53,-3.24, p <0.001). For every one day increase in physical activity in a week, reduces AGIS score by 0.20 (95% CI -0.23, -0.15). There was also a linear relationship seen between BMI and AGIS score (adjusted b 0.33, 95% CI 0.11, 0.56, p<0.001).

CONCLUSION

Cigarette smoking and physical activity are potential modifiable risk factor for severity of POAG. Cessation of cigarette smoking may help in halting the progression of visual field to more severe stage of glaucoma. Physical activity may protects against the severity of glaucoma. Longer duration of physical activities reduces the severity of POAG. It is recommended that POAG patients practice healthier life style with becoming more active and abstinence from smoking to prevent further damage of POAG.

CHAPTER 1

INTRODUCTION

INTRODUCTION

1.1 Primary open angle glaucoma

Glaucoma is the leading cause of irreversible blindness in the world (International Council of Ophthalmology, February 2016, Foster and Johnson, 2001). The diagnosis of glaucoma is based on intraocular pressure (IOP) measurement, optic disc evaluation, and producible visual field testing (Tuck and Crick, 1997). According to International Council of Ophthalmology (ICO), primary open angle glaucoma (POAG) can be defined with the presence of characteristic glaucomatous optic nerve damage in an open angle eye with no identifying pathology, with or without visual field damage and elevated intraocular pressure (International Council of Ophthalmology, February 2016). Based on World Glaucoma Association (WGA) consensus, clinical diagnosis of glaucoma is predicted on the detection of thinning of the retinal nerve fiber layer (RNFL), narrowing of the neuroretinal rim, and deformation of the optic nerve head (ONH) (cupping) (World Glaucoma Association 10th Consensus, April 2016).

World Glaucoma Association (WGA) consensus recommended that detection of progressive glaucomatous RNFL thinning and neuroretinal rim narrowing provide a standard assessment for glaucoma diagnosis (World Glaucoma Association 10th Consensus, April 2016). Optical Coherence Topography (OCT) measurement of RNFL thickness may be the best among the currently available digital imaging instruments for detection of glaucoma and progression of optic nerve damage in glaucoma (World Glaucoma Association 10th Consensus, April 2016). Perimetry assessment is indispensable for documentation and monitoring of function decline in glaucoma (World Glaucoma Association 10th Consensus, April 2016). Gonioscopic examination is essential in determine the status of the angle; open or closed angle glaucoma (Tuck and Crick, 1997).

1.2 Prevalence of POAG

1.2.1 Global prevalence of POAG

A survey by the World Health Organization (WHO) in 2002 demonstrated 37 million people were blind worldwide (Kingman, 2004). It has been estimated that glaucoma contributed to 12.3% of these blindness (Bourne, 2006). Quigley and Broman (2006) estimated that 8.4 million people were blind by glaucoma. It is estimated to escalate to 11.1 million people by year 2020 (Quigley and Broman, 2006).

POAG and primary angle closure glaucoma (PACG) are the commonest type of glaucoma. WHO estimated the number of people worldwide affected by glaucoma to be about 20 million in 1993 (Thylefors and Negrel, 1994). Out of these, POAG is responsible for 3.0 million global blindness and PACG is responsible for 2.0 million blindness worldwide. Three years, based on another survey, the estimation of prevalence of POAG and PACG escalated to 66.8 million people worldwide. The numbers of people affected by each disease were nearly equal in number (Quigley, 1996).

The prevalence rate of POAG is the highest amongst people of African origin, and lowest among Caucasians of European origin (Tielsch et al., 1991, Friedman et al., 2006). The rate of POAG in Asian populations are intermediate between these two groups (South East Asia Glaucoma Interest Group, 2008). Based on a systemic review and meta-analysis, the overall global prevalence of glaucoma was 3.54% with POAG contribute 3.05% (out of 3.54%) (Tham et al., 2014). POAG is the disease of longevity. For every decade increase in age, the prevalence increases 1.73 folds (95 % CI, 1.63-1.82) (Tham et al., 2014). Men are more at risk. Men have 1.36 folds risk (95% CI, 1.23-1.52) to develop POAG compared to women (Tham et al, 2014). Tham et al (2014)

also found that those living in urban area are more at risk to develop POAG (OR 1.58; 95% CI, 1.19-2.04) (Tham et al., 2014). The differences in prevalence of glaucoma between a rural and urban areas may be due to lifestyle; stress, smoking, physical activities, and comorbid disease (Tham et al., 2014).

1.2.2 Prevalence of POAG in Chinese population

Chinese is identified as the world's largest ethnic group which is more than 1.3 billion peoples (source from United Nation population division: World populous prospect, 2013 Census ethnic group profile; stats.govt.). In fact, Chinese people can be seen everywhere across the world. The Chinese peoples have a long history of migrating overseas. They are defined as people of Chinese birth or descent who live outside of People's Republic of China, Taiwan, Hong Kong and Macau also known as the oversea Chinese. Majority of them are from Han Chinese sub-ethnic group (Barabantseva, 2011). Their history started during Ming dynasty (1371-1435) when Zheng He sent Chinese people to expand their trading ventures in the South China Sea and in the Indian Ocean area (Pan, 1999) . The second wave of migration occurs during Chinese Civil War in 1949. After Nationalist government lost to Communist Party, many Chinese peoples fled the mainland of China and settled down in South East Asia (Singapore, Malaysia and Indonesia). These migrants gain citizenship in Malaysia and Singapore automatically in 1957 and 1963 as these countries gained independence (Suryadinata, 2007).

Based on the National Census of Malaysia in 2010, reported 6.6 million Chinese ethnic group reside in Malaysia (Department of Statistics Malaysia, 2012). The migrations of Chinese people to the countries in North America and Australasia started due to great demand of laborers were needed in gold mining and railway construction (Pan, 1999).

After World War II, many Chinese peoples emigrated to England and Netherlands to earn a better living (Tan, 2013). From mid-19th century onward, emigration has been directed to other Western countries such as United States, Canada, Australia, New Zealand and nations of Western Europe. In 1984 after Britain agreed to transfer the sovereignty of Hong Kong to Republic of China, had triggered another wave of migration to the Western country mainly England (Pan, 1999).

A decade ago, data on the prevalence of glaucoma affecting Asian people appeared to be contradictory between population study (Foster and Johnson, 2001). In China alone, nearly 10 million people diagnosed to have glaucoma (Foster and Johnson, 2001). Approximately 5.2 million people diagnosed with glaucoma are blind in at least 1 eye, and 1.7 million blind in both eyes (Foster and Johnson, 2001). The exact difference between rate of POAG and PACG in Asian particularly China is difficult to determine. According to SEAGIG in Asia Pacific Glaucoma Guidelines 2008, the higher rate of glaucoma in China is attributable by primary angle closure glaucoma (PACG) (South East Asia Glaucoma Interest Group, 2008). Data from meta-analysis in 2013 showed that Asia accounts for 53.4% of worldwide POAG cases and 76.7% of PACG cases worldwide (Tham et al., 2014).

Epidemiological studies done in Asia revealed the prevalence of POAG in Asia range from 0.5% to 3.9% (He et al., 2006, Sun et al., 2012, Baskaran et al., 2015, Foster et al., 2000). Foster and Johnson (2001) estimated 1.7 million in rural area and 1.8 million in urban China were affected by POAG. POAG was found to be responsible for 909 500 cases of blindness in China. Their data was based on their extrapolation of data from epidemiological study in Mongolia (Foster et al., 1996) and Singapore (Foster et al., 2000).

1.3 Glaucoma progression and severity

Glaucoma is a chronic progressive disease causing optic nerve head damage that requires lifetime monitoring (Brusini and Johnson, 2007). Glaucomatous damage can be quantified using either structural (optic nerve damage) or functional loss criteria (visual field defects), or a combination of both (Brusini and Johnson, 2007, Medeiros et al., 2012a). Progression rates are highly variable among patients (Leske et al., 2007, Rossetti et al., 2010). Disease progression in glaucoma is common and despite treatment, most patients still progress (Rossetti et al., 2010).

In Early Manifest Glaucoma Treatment (EMGT) study, 76% and 59% of patients progressed in the untreated and treated cohorts respectively over eight years of follow-up (Leske et al., 2003, Leskea et al., 2004). In clinical practice, determination of progression is mostly relies upon serial visual fields (functional) assessment (Kirwan et al., 2014). Detection of early glaucoma damage also can be done by serial evaluation of longitudinal series of visual field test (Giangiacomo et al., 2006). For many years, Standard Automated Perimetry (SAP) is the most common method for assessing visual field (VF) in glaucoma (Chauhan et al., 2008, Heijl, 1989). SAP also can be used to measure the rate of glaucoma progression. Many clinical trials in glaucoma used only SAP as primary endpoint to measure disease progression (Chauhan et al., 2008). It was been recommended as in European Glaucoma Society, Guidelines (Terminology and Guidelines for Glaucoma; 4th Edition) to measure the rate of VF progression in daily clinical practice (Augusto Azuara Blanco, 2014).

Visual field progression can be evaluated using trend analysis and event-based analysis (Birch et al., 1995, Heijl et al., 2002, Spry and Johnson, 2002, Diaz-Aleman et al., 2009). Trend analysis include mean deviation index (MDI). MDI calculation from the

Humphrey visual field perimetry has become a standard index for estimating the glaucoma progression rate (Casas-Llera et al., 2009). However, this trend analysis of MDI calculation is poorly correlated with clinical judgement (Arnalich-Montiel et al., 2009), because the MDI is affected not only by increasing glaucoma progression and severity, but also by cataract. Increasing cataract can falsely suggest a high glaucoma progression rate (Klein et al., 1996, Koucheki et al., 2004, Heijl et al., 1987). The MDI values will improve after cataract extraction thus jeopardising further evaluation and monitoring of glaucoma progression (Klein et al., 1996, Koucheki et al., 2004). The other weakness is that MDI is very weakly center weighted, therefore it is not well correlated to patient real visual function (Heijl et al., 1987).

The event-based analysis is primarily to detect whether progression has occurred (Caprioli, 2008). Glaucoma progression analysis (GPA) software incorporated in Humphrey Visual Field Analyser (VFA) (Carl-Zeiss Meditec, Dublin, CA) is one of the example of event-based analysis (Casas-Llera et al., 2009). This software will give an analysis of pattern standard deviation (PSD) values (Casas-Llera et al., 2009). This allowed monitoring of glaucoma progression Visual filed index (VFI) to measure the rate of VF progression was introduced recently (Bengtsson and Heijl, 2008). VFI is based largely on Pattern Standard Deviation (PSD) analysis but displays in the form of linear regression (Casas-Llera et al., 2009, Bengtsson and Heijl, 2008). It was found that VFI analysis is more accurate than MD analysis for determining rate of progression (Casas-Llera et al., 2009).

The event-based analysis, Glaucoma progression analysis (GPA) detected progression earlier (about 7 months) compared to trend VFI analysis (Casas-Llera et al., 2009). Trend-based analysis (VFI) requires larger number of Humphrey visual field (HVF) test to detect progression (Caprioli, 2008). A primary limitation of event-based analysis

is in detecting progression of defect within the central 10 degree (Diaz-Aleman et al., 2009, Arnalich-Montiel et al., 2009).

Structural changes of optic nerve head (ONH) is part of the criteria of the progression. The advancement of ophthalmic imaging has introduced optical coherence tomography (OCT) and Heidelberg retinal tomograph (HRT) in detection of progression of glaucoma. These technologies enable quantitative imaging of the ONH, retinal nerve fiber layer (RNFL) and inner macular layer (Kirwan et al., 2014, Medeiros et al., 2012b). However, these technologies are expensive and is not accessible to many ophthalmologists (Brusini and Johnson, 2007). The determination of progression also should not merely based on these quantitative images alone. It is best to determine progression on the agreement between structural progression and functional deterioration (Musch et al., 2009, Kirwan et al., 2014, Bengtsson and Heijl, 2008, Leung et al., 2010, Wilson et al., 1982, Medeiros et al., 2012a).

Standardization of glaucoma severity scoring is paramount to provide a common understanding for both clinical and research purposes (Susanna Jr and Vessani, 2009). Staging the severity into appropriate categories enhances management of the glaucoma towards personalized treatment (Susanna Jr and Vessani, 2009). Staging of glaucoma can be divided into mild, moderate and advanced/severe based on structural damage and extension of the visual field defects.

Serial HVF evaluation is currently the most common method used to quantify glaucomatous damage (Brusini and Johnson, 2007). HVF has the capability to quantify the severity as the baseline and subsequently determine the progression after serial HVF assessment during a certain period of time (Susanna Jr and Vessani, 2009). Analysis of structural damage (optic disc and nerve fiber layer) to quantify the severity of

glaucoma still under evaluation (Brusini and Johnson, 2007). Numerous example of staging systems using Standard Automated Perimetry have been proposed such as Author n and Karmeyer's method (Greve, 1982), Functional Vision Score system (Colenbrander et al., 1992), Quigley's Grading scale (Quigley et al., 1996), Hodapp, Parrish and Anderson's classification (H-P-A) (Hodapp et al., 1993), Glaucoma Staging System (GSS); modified of H-P-A (Brusini, 1995), the Advance Glaucoma Intervention Study (AGIS) (Investigators, 1994).

Generally, staging of the severity based on the visual field defect involves either the number and depth of defective points, or based on HVF visual field indices; mean deviation (MD), corrected pattern standard deviation (CPSD) (Brusini and Johnson, 2007).

Hodapp, Parish and Anderson (H-P-A) criteria is based on two criteria; the first criterion looking to the extent of damage (using Mean Deviation (MD) value and the number of defective points in Humphrey Statpac-2 pattern deviation probability map of the 24-2 SITASTANDARD or the 30-2 full threshold test; second criterion is based on the defect proximity to the fixation point (Ng et al., 2012). It has gained popularity due to the ease in application clinically. However, it is time-consuming analysis and no information about location and depth of the defects. Another drawback is this system may suggest a significant deterioration when in fact none has occurred (Susanna Jr and Vessani, 2009).

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, 1994, Brusini and Filacorda, 2006). 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, 1994). This staging system is almost accurate and provide standardized classification of visual field according to severity. 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).

The Glaucoma Staging Systems (GSS) introduced by Brusini (Brusini, 1995) uses MD and CPSD values from HVF and plot the values on a Cartesian coordinate diagram. Stage of glaucoma damage can be determined by the intersection of MD and CPSD values on the diagram. Stage is divided into Stage 0 (normal visual field) to stage 5 (only small remnants of sensitivity remaining). GSS not merely provide information of stage of glaucoma damage but the type of the damage whether generalized, mixed or focal is also identified. GSS is quick and able to provide the specific visual field damage (Koçak et al., 1996). However, GSS is unable to provide information on location, shape or morphology of the visual field defects.

Enhanced GSS (e-GSS) is a modified GSS (Brusini and Filacorda, 2006). This classification is an improved system of GSS. The major limitation of GSS; non-mutually exclusive criteria between stages (narrow band between stage 0 and stage 1), and 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 Bebie curve

(Brusini and Filacorda, 2006). e-GSS is applicable many available software (Brusini and Filacorda, 2006).

1.4 Risk factors for POAG progression

Risk factors for POAG can be divided into non-modifiable and modifiable risk factors. Non-modifiable risk factors are genetic, age, gender, race and pre-existing eyes structures for example a thick central corneal thickness (CCT), long axial length and refractive error for example moderate to high myopia (GARG et al., Doshi et al., 2008, Chihara et al., 1997, Kaimbo et al., 2001, Leske et al., 1995, Coleman and Miglior, 2008, Anne and Gergana, 2009, Boland and Quigley, 2007). Elevated intraocular pressure (IOP), was the only modifiable risk factor (Anne and Gergana, 2009). However, recently emerging research indicates that modifiable risk factors other than IOP may be associated with the presence and/or progression of glaucoma (GARG et al., Boland and Quigley, 2007, de Voogd et al., 2006, Werne et al., 2008, Chang et al., 2010).

A systemic review on assessment of risk factors for the progression of glaucoma based on several clinical trials, population-based cohort studies and large retrospective studies had been done (Friedman et al., 2004). They summarized the risk factors for progression of glaucoma include; (i) age; studies supported this were Advanced Glaucoma Intervention Study (AGIS), Collaborative Initial Glaucoma Treatment Study (CIGTS) and Early Manifest Glaucoma Trial (EMGT) (ii) diabetes mellitus; supported by AGIS and CIGTS (iii) disc haemorrhage; in Collaborative Normal Tension Glaucoma Study (CNTGS) and EMGT (iii) female; as a risk factor found in CNTGS. Study who found the association of male with progression of glaucoma was the AGIS (iv) higher IOP at the onset; described in EMGT, however higher IOP over the follow-up found as one of the risk factor in CNTGS and EMGT (v) race as risk factor was

explained by CIGTS who found black as a high risk factor, and Asian people as a risk factor demonstrated by CNTGS (vi) baseline visual field as a risk factor found in EMGT. Of all the risk factors mentioned in this systemic review, the modifiable recognized risk factors were diabetes mellitus and the IOP (Friedman et al., 2004).

Other authors had hypothesized POAG risk factors includes: glaucoma family history (Tielsch et al., 1991), body mass index (BMI) (Berdahl et al., 2012, Pasquale and Kang, 2009, Pasquale et al., 2010), mean arterial blood pressure (Werne et al., 2008, Bulpitt et al., 1975, Xu et al., 2007), physical activity (Williams, 2009), cigarette smoking (Wang et al., 2012, Edwards et al., 2008, Lee et al., 2003, Bonovas et al., 2004, Chiotoroiu et al., 2013, Williamson et al., 1995, Takashima et al., 2002, Kang et al., 2003, Shields, 2004), caffeine (Pasquale and Kang, 2009, Kang et al., 2008, Chandrasekaran et al., 2005, Higginbotham et al., 1989) and alcohol intake (Chiotoroiu et al., 2013, Klein et al., 1993). From these studies of risk factors, glaucoma family history is non-modifiable risk factors. But the rest are modifiable and strongly related with our life-styles. Most importantly, these studies were validated studies with a high degree of reliability and accuracy of information (Friedman et al., 2004).

A clear understanding of modifiable risk factors would promote greater public and medical awareness for prevention programs, early recognition of this insidious disease and provide possibility of halting progression of glaucomatous field damage despite IOP normalization. However, there is still inconclusive evidence regarding many proposed these risk factors. We are not discussing of all mentioned modifiable risk factors, but we are focusing on association of smoking and physical activities on POAG, as our two specific objectives.

1.5 Cigarette smoking

1.5.1 Content of cigarette and the effects of cigarette on health

It is known that cigarette smokes is a risk factor for cardiovascular disease, diabetes mellitus and development of cancer (Menvielle G et al, 2009; Gallo V et al, 2009). Cigarette smoke is also identified as the risk for ocular diseases such as age-related macular degeneration, worsening thyroid eye disease, cataract, and glaucoma (Solberg et al., 1998, Cheng et al., 2000). The detrimental effect of cigarette smoking can be seen as an acute or long-term exposure (Solberg et al., 1998). The postulation of toxic effect to ocular tissues mainly through ischemic or oxidative mechanism (Solberg et al., 1998).

There are approximately 600 ingredients in a cigarette (tar phase), which create more than 7000 chemicals when burned (gas phase) (American Lung Association, 2016). These include acetone, ammonia, arsenic, benzene, butane, cadmium, carbon monoxide, formaldehyde, lead, methanol, nicotine and tar, just to name a few (American Lung Association, 2016). Mainstream smoke is a cigarette content that is drawn through the tobacco into a smoker's mouth. Side-stream smoke is the smoke emitted from burning ends of a cigarette. Mainstream cigarette content comprised of 8% of tar and 92% of poisonous gases components (Pryor and Stone, 1993). Side-stream cigarette content contains higher concentration of these poisonous or toxic gases than mainstream smoking (Glantz and Parmley, 1991).

Cigarette smoking promotes atherosclerosis of aortic and peripheral vessels (Price et al., 1999). Vasomotor dysfunction, inflammation, and modification of lipid by cigarette smoking are integral components for initiation and progression of atherosclerosis (Ross, 1999, Clarkson et al., 1987). Vasomotor dysfunction has been postulated as part

of vascular theory for pathogenesis of glaucoma (Su et al., 2008, Moore et al., 2008). Nitric oxide (NO) is a free radical that primarily responsible for the vasodilatory function of endothelium (Napoli and Ignarro, 2001). Cigarette smoke is associated with decreased availability of NO leading to vasodilatory dysfunction (Mayhan and Sharpe, 1996, Ota et al., 1997). Cigarette smoking is responsible in entire process of atherosclerosis; from initial endothelial dysfunction to acute clinical events due to thrombotic embolism (Ambrose and Barua, 2004).

Free radical in the cigarette may arise from both tar phase and gas phase (Pryor and Stone, 1993). The detrimental effect of these free radical include endothelial dysfunction, pro-inflammatory effects on the vessels wall, pro-thrombotic effects, reduce fibrinolysis, and lipid peroxidation(Pryor and Stone, 1993, Powell, 1998). Recently, free radical-mediated oxidative stress is known as the pivotal step for development of atherosclerosis (Gibbons and Dzau, 1994, Kojda and Harrison, 1999, Nedeljkovic et al., 2003). The negative effects of these free radicals further increase atherosclerosis and vascular dysfunction.

Both active and passive cigarette smokers are predisposed to cardiovascular events (Ambrose and Barua, 2004). Correlation between direct dose-dependent of cigarette and the risk of development of diseases still debatable. Recent experimental clinical studies have shown a non-linear relation between two (Ambrose and Barua, 2004). Even those who smoked low-tar cigarettes and smokeless tobacco are at increased risk of cardiovascular events compared to non-smokers (Negri et al., 1993, Bolinder et al., 1994). Passive smoker that is exposed to one-hundredth of the exposure of smoker has30% increased risk of coronary artery disease (CAD) compared to active smoker (Glantz and Parmley, 1991, Law et al., 1997). Active smokers have 80% risk of cardiovascular event (Ambrose and Barua, 2004).

1.5.2 Cigarette smoking in Malaysian population

Based on the 3rd National Health and Morbidity Surveys (NHMS III) in 2006, the prevalence of active smoking among adult males in Malaysia was 46.4% (Institute of Public Health, 2008). An approximately 36.0% of smokers were Chinese (Institute of Public Health, 2008). This percentage of smoker was higher than rates from the Global Adult Tobacco Survey (GATS) conducted 5 years later in 2011. Based on GATS, 43.6% of Malaysian male aged 15 years and above were active smoker (Lim et al., 2013). The difference may be due to under reporting case in GATS. In fact this rate showed a true drop in prevalence of smoker as a result proper health education and healthy life style campaign (Lim et al., 2013).

NMHS III (2013) reported the age of smoking onset between 16-18 year old as compared to NHMS II in 1996. NHMS II (1996) reported the age of smoking onset between 17 to 19 year old. Similar smoking habit surveys in a developed countries found the mean age of onset of smoking was older compared to Malaysia (Lim et al., 2013). Based on NHMS III, the average number of cigarettes smoked by Malaysians were 12.3 cigarettes per day. The NHMS III also found the higher proportion of ex-smoker in older age groups. Lung cancer and cardiovascular disease, chronic respiratory disease, and stroke are still the main smoking-related diseases (Osler et al., 1998, Ezzati and Lopez, 2003, Health and Services, 2004).

1.5.3 The effect of cigarette smoking on POAG

Active smoker was found to have higher IOP compared to non-smokers based on the Blue Mountains Eye Study (Lee et al, 2003). It remained significantly higher even after adjustment with blood pressure, diabetes, myopia, family history and pseudo-exfoliation (Lee et al., 2003). Cigarette smoking may affect the IOP by aqueous

dynamics disturbances and its atherosclerotic and thrombotic effects on the ocular capillaries (Cheng et al., 2000). Furthermore cigarette smoking enhances the generation of free radicals, thus reduces the level of antioxidants in the blood circulation, aqueous humour, and ocular tissue (Cheng et al., 2000). This oxidative stress will further damage the ocular tissue and particularly ganglion cells in optic nerve head to accelerate damage of glaucoma (Cheng et al., 2000).

The exact toxic components of cigarette smoking and the mechanism involved in cigarette smoking related ocular diseases is still largely unknown. The high concentration of free radicals in particulate (tar) and gas phases believed to play an important role (Ambrose and Barua, 2004). Apart from the direct effect of free radicals from the cigarette, free radicals also cause activation of endogenous source of free radicals (eg. Nitric oxide synthase (NOS), xanthine oxidase, and nicotinide adenine dinucleotide phosphate (NADPH) oxidase etc) from smoking lead to increase in oxidative stress, reduction nitric oxide (NO) generation and bioavailability, and activation of inflammation process in initiation and progression of tissue damage (Ambrose and Barua, 2004).

According to Basic Eye Health (2005), toxins associated with smoking may decrease blood flow or formation of clot in ocular capillaries. Inadequate blood flow reduces vascular supply of nutrient and oxygen to optic nerve head causing glaucomatous neuropathy. The role of carbon monoxide (CO) in cigarette smokers an athero-thrombotic agent found to be equivocal (Ambrose and Barua, 2004). Free-radical-mediated oxidative stress in cigarette smoking play a pivotal step for development of atherosclerosis (Gibbons and Dzau, 1994, Kojda and Harrison, 1999, Nedeljkovic et al., 2003). Free radicals such as superoxide in the cigarette decreases NO availability (Kojda and Harrison, 1999). NO is responsible for the vasodilatory function of the

endothelium (Napoli and Ignarro, 2001). Toxic effect of free radical in the cigarette may cause pro-atherogenic and/or pro-thrombotic effect and vasodilatory dysfunction further compromised blood flow to retina and retinal nerve fiber layer of ONH. This may perhaps accelerate the glaucomatous damage.

Timothy et al in their clinical study demonstrated cigarette smoking has a strong effect on intra-ocular pressure in normotensive individual. They also found positive effect of smoking with the systolic blood pressure readings (Timothy and Nneli, 2007). There is consistent association between the degree of arterial blood pressure and elevation of IOP (Smith et al., 2004, Tanabe et al., 2010, Sharrett et al., 1999). Smoking is significantly associated with elevated IOP in Japanese men (Yoshida et al., 2003). Fluctuation and uncontrolled IOP may also influence the progression of visual fields defects and development of more severe stage of glaucoma.

A meta-analysis involving seven reports found significant association of cigarette smoking and risk of POAG (Bonovas et al., 2004). On contrary, a systematic review involved 11 papers; 9 case-control studies, 1 prospective cohort study and a paper describing a pooled analysis based on 2 prospective cohort studies, found minimal evidence association between smoking and development of POAG (Edwards et al., 2008). In addition, a large prospective study involving female nurses and male health professionals found that cigarette smoking is not a risk factor for development of POAG (Kang et al, 2003). However, there was a modest inverse association of pack-years of smoking with risk of glaucoma; those who smoked 30 or more pack-years have a 22% reduced risk of POAG (relative risk, 0.78; 95% CI, 0.55-1.11) compared to those who have never smoked (Kang et al., 2003). However, this study involved medical health professions who by virtue of their work may have practiced healthy lifestyle such as physical activity and better nutrient or anti-oxidant supplement.

In another study, there was no significant association between cigarette smoking and onset of open angle glaucoma in adult POAG and juvenile open angle glaucoma (Wang et al, 2012). Wang and associates (2012) found a significant association of smoking with reduction in central cornea thickness (CCT). Perhaps, this will affect the IOP measurement and diagnosis of POAG.

1.6 Physical activities

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, and thus is a fundamental to energy balance and weight control (World Health Organization (WHO) 2015). Physical activity includes recreational or leisure-time physical activity, transportation (e.g walking or cycling), occupational (i.e. work), house-hold chores and sports or planned exercise (World Health Organization (WHO) 2015).

Exercise or physical activity can be classified into as aerobic and anaerobic. In general, aerobic exercise involves activities that burn glycogen and fat for energy. An aerobic physical activity requires low to moderate level of exertion. Lactic acid is not produced with aerobic exercise. Common types of aerobic exercise include running, biking or swimming (Donatelle, Rendi et al., 2008). On the other hand, anaerobic exercise is high intensity exercise, involved builds up lactic acid in the body causing discomfort and fatigue during this exercise. Example of this type of exercise is weight lifting (Rendi et al., 2008, Donatelle).

Physical activity is also defined based on the stress to cardiovascular systems. Based on this definition, physical activity is divided into isometric (static) or isotonic (dynamic) (Rowell, 1986). Isometric exercise is defined as a constant muscular contraction without movement (static) e.g handgrip. This type of exercise imposed

greater pressure than volume load on the cardiac output. While isotonic (dynamic) exercise is defined as muscular contraction resulting in movement. Isotonic exercise causes volume load to heart and the cardiovascular response is proportionate to intensity of exercise (Fletcher et al., 1992).

Physical activity can help control blood lipid abnormalities, diabetes, obesity and provide blood pressure lowering effect (especially the aerobic exercise) (Martin et al., 1990, Hagberg et al., 1989, Jennings et al., 1989). Physical activity also provides beneficial effects to hemodynamics circulation, hormonal, metabolic, and respiratory function. The beneficial effect of physical activities is exponential to the degree of exercise (Fletcher et al., 1992).

There are also changes in oxidative stress level related to exercise. Lipid peroxidation increases immediately post-exercise for both aerobic and anaerobic exercise (Bloomer et al., 2005). While gluthathione oxidation increases immediately post aerobic exercise only (Bloomer et al, 2005). Oxidative stress is known to further accelerate glaucoma optic neuropathy either directly or from high IOP (Izzotti et al., 2006). Thus, physical activity may help in reduction of oxidative stress level.

1.6.1 The association between physical activities and POAG

Physical activity is associated with reduction of IOP (Kielar et al., 1975, Williams, 2009, Qureshi, 1997, Yip et al., 2011). However, there were evidences of temporary elevation of IOP during initial part of exercise (Forth et al., 1984, Yamabayashi et al., 1991). The immediate rise in IOP at the initial time of exercise is due to contraction of abdominal and thoracic muscles, changes in body position or related to valsalva manoeuver (Porth et al., 1984).

There are many postulations how the physical activity reduce the IOP. These include changes in the episcleral venous pressure (Risner et al., 2009), lower the blood flow (Jennings et al., 1989), changes in the plasma lactate levels and blood pH (Kielar et al., 1975), changes in the plasma osmolarity (Ashkenazi et al., 1992), and hormones changes (serum norepinephrine) (Stewart et al., 1970), changes in aqueous dynamics (Stewart et al., 1970), and increase in outflow facility of aqueous through increased systemic fibrinolytic activity (Biggs et al., 1947, PANDOLFI and KWAAN, 1967). However, the exact mechanism still under investigation.

There was direct relationship between the intensity of physical activity or exercise and the total energy consumption with IOP reduction (Avunduk et al., 1999, Williams, 2009, Kielar et al., 1975, Harris et al., 1994, Kiuchi et al., 1993, Qureshi, 1995a). However the exact mechanism is not fully understood. Qureshi et al (1995a) observed that all forms of physical activity decreased IOP. A greater fall in IOP was seen with increased intensity of physical activity (Qureshi, 1995a). Qureshi et al (1995a) also found that the effect was more prominent in glaucoma patients compared to normal subjects. This could be due to the higher initial IOP is associated with a greater reduction in IOP post exercise. A longer duration of post-exercise recovery of IOP was also observed in glaucoma patients(Qureshi, 1995b). However, this effect needs further evaluation.

Other than IOP, impaired ocular perfusion pressure (OPP) also seems to be a risk factor for POAG (Flammer et al., 2002). In the eye, venous pressure is equal to or slightly higher than IOP (Glucksberg and Dunn, 1993, Mäepea, 1992). Thus, ocular perfusion pressure (OPP) can be estimated as the difference between arterial blood pressure and IOP. Therefore, high IOP and low systemic blood pressure may lead to reduce OPP (Leske, 2009, Schmidl et al., 2011, Werne et al., 2008). Physical activity was found to

increase OPP (Kiss et al., 2001, Risner et al., 2009). Systemic blood pressure increases following physical activity. An increase in systemic blood pressure leads to an increase in OPP. Both isometric and isokinetic exercise have been shown to increase systemic blood pressure, thus invariably improves OPP and optic nerve head circulation. Theoretically, will prevent further deterioration of glaucomatous damage in POAG patients.

1.7 Rationale of study

Malaysia is a multi-racial country which consists of three main ethnicities. The prevalence of glaucoma, as well as its severity, may vary between these races. Glaucoma is a complex disease with the interplay between genetics and environmental factor. In 2010, the population of Chinese was 24.6%, comprising the second largest ethnic group after Malays and Bumiputeras (60.3%) (Department of Statistics Malaysia, updated 2 July 2010). Malaysian Chinese are people of full or partial Chinese descent, particularly Han Chinese ancestry, who immigrated to Malaysia during the Malacca Empire in the early 15th century. The second wave of Chinese immigrants was in the 19th century, mainly from Fujian and Guangdong who were attracted by the prospect of work in the tin mines and rubber plantations. These immigrants from Fujian generally identify as Hokkien; as they speak Hokkien. However, newer generations of Malaysian Chinese are usually bilingual and can speak English or Bahasa Malaysia.

There were various studies conducted among Chinese in various part of the world (refs please). Chinese may share genetics similarities regardless where they resided. However, we believed that environmental different may alter the clinical presentation of glaucoma. This current study is part of Chinese Glaucoma Eye Study (ChiGES). ChiGES is a collaborative research project between universities and Ministry of Health

in Malaysia. The main aim of ChiGES is to identify potential modifiable risk factors for severity and progression of primary glaucoma. The modifiable risk factors include cigarette smoking and physical activities. To the best of our knowledge, there is no study that assesses the relationship between smoking and physical activity with severity of POAG. Identification of modifier risk factor is important to improve the management of glaucoma and the development of new drugs in the future.

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