

ASSOCIATION OF CIGARETTE SMOKING AND PHYSICAL ACTIVITY WITH PRIMARY ANGLE CLOSURE GLAUCOMA IN MALAY PATIENTS

By

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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 acknowledge.

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ABSTRAK

PENGENALAN

Glaukoma sudut tertutup primer (GSTP) didapati mempunyai prevalen yang tinggi di kalangan penduduk Asia Tenggara dan mengakibatkan kebutaan yang signifikan. Penyakit ini tidak asing bagi kaum Melayu, namun maklumat berkenaan penyakit ini dikalangan pesakit Melayu adalah sangat terhad. Dewasa ini, satu-satunya faktor bolehubah untuk mengurangkan risiko penyakit GSTP adalah tekanan intraokular. Tabiat merokok dan aktiviti fizikal adalah berpotensi sebagai faktor bolehubah. Kajian sebelum ini telah menunjukkan potensi kaitan antara kedua-dua aspek tersebut dengan kerosakan akibat pengoksidaan, perubahan kepada tekanan intraokular, serta perubahan kepada perfusi okular yang dikaitkan dengan patogenesis penyakit glaukoma.

OBJEKTIF

Kajian ini dijalankan untuk mengenalpasti perkaitan antara tabiat merokok dan aktiviti fizikal dengan GSTP di kalangan kaum Melayu.

KAEDAH KAJIAN

Satu kajian rentas telah dijalankan yang melibatkan dua ratus pesakit GSTP berbangsa Melayu dan dua ratus lima puluh subjek berbangsa Melayu yang normal. Pesakit GSTP adalah dipilih berdasarkan kebolehtutupan sudut mata serta kewujudan ciri-ciri yang menunjukkan berlakunya sumbatan pada jaringan trabekular pada atau lebih

daripada 270° iris bahagian periferi beserta bukti kerosakan pada saraf optik atau medan penglihatan yang berpunca daripada glaucoma; iaitu berdasarkan kriteria diagnosis yang digariskan oleh Kesatuan Glaukoma Sedunia (*World Glaucoma Association*). Pesakit yang disyaki mengalami sudut mata tertutup primer, serta pesakit yang disyaki meghidap glaukoma dikecualikan daripada kajian. Pesakit yang mengalami masalah yang mungkin mempengaruhi medan penglihatan seperti masalah retina dan masalah neurologi juga dikecualikan. Turut dikecualikan adalah pesakit yang mengalami masalah strok, serta masalah daya ingatan, termasuk dementia. Carta keturunan juga dilukis. Pesakit yang terdiri daripada sekurang-kurangnya tiga lajur keturunan Melayu diterima sebagai subjek. Temuduga secara bersemuka dijalankan untuk mengenalpasti tabiat merokok serta tahap aktiviti fizikal mereka. Status tabiat merokok didokumentasi dengan menggunakan soalselidik “*Singapore Malay Eye Studies*” (SiMES) manakala penilaian aktiviti fizikal didokumentasikan dengan menggunakan “*International Physical Activity Questionnaire (IPAQ)*” yang telah divalidasikan dalam versi Bahasa Malaysia dan digredkan berdasarkan protokol pemarkahan IPAQ. Analisa univariansi dilakukan untuk mengenalpasti faktor lain yang berkaitan dengan GSTP. Perkaitan antara tabiat merokok dan aktiviti fizikal dengan GSTP dianalisa dengan “*multiple logistic regression*”. Faktor yang boleh mempengaruhi seperti usia, jantina, tahap pendidikan serta indeks jisim tubuh disertakan dalam analisa.

KEPUTUSAN

Sejumlah 255 wanita dan 195 lelaki telah menyertai kajian ini. Terdapat perbezaan yang signifikan pada pembahagian jantina antara pesakit GSTP dengan subjek

kawalan ($p < 0.001$). Nisbah antara pesakit wanita kepada pesakit lelaki GSTP ialah 3.88:1. Perokok pasif didapati mempunyai hubungan yang signifikan dengan GSTP ($p < 0.001$ OR: 6.82 CI 2.49, 18.67). Namun, di kalangan perokok, jumlah rokok yang diambil tiada perkaitan yang signifikan dengan GSTP ($p = 0.144$), termasuklah tempoh merokok ($p = 0.176$). Aktiviti fizikal yang sederhana dan rendah mengurangkan risiko GSTP sebanyak 77% ($p < 0.001$, 95% CI 0.10, 0.52), dan 79% ($p = 0.001$, 95% CI 0.009, 0.53). Namun, tiada perbezaan yang signifikan antara GSTP dan subjek kawalan dari aspek bilangan hari aktif dalam seminggu ($p = 0.851$, 95% CI 0.85, 1.14) atau dari aspek jumlah minit aktiviti sehari ($p = 0.949$, 95% CI 0.99, 1.00). Tahap pendidikan yang lebih rendah adalah berkaitan dengan risiko yang lebih tinggi terhadap GSTP. Berbanding golongan yang menerima pendidikan tertier, golongan yang menerima pendidikan sekunder berisiko mengalami GSTP sebanyak 9 kali ganda (95% CI 2.67, 33.04), manakala golongan yang menerima pendidikan primer berisiko mendapat GSTP sebanyak 18 kali ganda (95% CI 4.53, 73.95). Golongan yang tidak menerima sebarang pendidikan formal berisiko sebanyak 48 kali ganda untuk mendapat GSTP (95% CI 8.3, 277.99).

KESIMPULAN

Pengubahsuaian cara hidup merupakan faktor yang berpotensi untuk menurunkan risiko penyakit GSTP di kalangan Melayu. Penghindaran dari persekitaran merokok serta peningkatan dalam aktiviti fizikal berkemungkinan dapat mencegah penyakit GSTP.

ABSTRACT

INTRODUCTION

Primary angle closure glaucoma (PACG) has relatively high prevalence in Southeast Asia and responsible significantly for blindness. This disease is not uncommon among Malays, but there is limited information related to this disease among Malays. At present, the only modifiable risk factor for PACG is intraocular pressure (IOP). Cigarette smoking and physical activities are potential modifiable factors. Previous studies had shown potential association of cigarette smoking and physical activities with oxidative damage, alteration of IOP, and changes of ocular perfusion. These mechanisms may play important role in the pathogenesis of glaucoma.

OBJECTIVE

To determine the association between smoking and physical activity level and PACG in Malays.

METHODOLOGY

A cross sectional study was conducted involving 200 Malay PACG patients and 250 control subjects. PACG is diagnosed in the presence of occludable draining angle and features indicating that trabecular obstruction by equivalent to or more than 270° of peripheral iris with evidence of glaucomatous optic disc and visual field damage, based on the World Glaucoma Association consensus. Primary angle closure suspect (PACS), primary angle closure (PAC) and glaucoma suspect patients were excluded

from the study. Patients with conditions that may affect the visual field such as retinal diseases and neurological diseases were excluded. Those with history of cerebral vascular accident and memory problem including dementia were also excluded. Pedigree chart was also drawn. Those with three generation of Malay lineage without any interracial marriage are included. Face to face interview was conducted to determine the smoking status and physical activity of the recruited patients. Validated questionnaire from Singapore Malay Eye Studies (SiMES) and Bahasa Malaysia version of International Physical Activity Questionnaire (IPAQ) was used. The number of cigarettes smoked per day, frequency and duration of physical activities was also derived from the questionnaires. Univariate analysis was done to identify other risk factors associated with PACG. The association of smoking and physical activity level and PACG was analysed with multiple logistic regression. Confounders such as age, gender, education status, and body mass index were considered in the analysis.

RESULTS

A total of 255 female and 195 male were included in this study. There was significant difference in sex distribution between PACG patients and control subjects ($p < 0.001$). There was 3.88:1 in female to male ratio among PACG patients. Passive smoking is significantly associated with PACG ($p < 0.001$ OR: 6.82 CI 2.49, 18.67). However, among smokers, the amount of cigarette ($p = 0.144$) and duration of smoking ($p = 0.176$) is not associated with PACG. Moderate and low physical activity reduces the risk for PACG by 77% ($p < 0.001$, 95% CI 0.10, 0.52) and 79% ($p = 0.001$, 95% CI 0.09, 0.53) respectively. However, there was no significant difference in days per

week of physical activity ($p = 0.861$), and minutes per day of physical activity ($p = 0.241$) between PACG and control subjects. Lower education status is associated with higher risk of PACG. Compared to those with tertiary education, secondary level of education significantly increase the risk for PACG by 9 folds (95% CI 2.67, 33.04) while primary level of education increase the risk for PACG by 18 folds (95% CI 4.53, 73.95) and those without formal education has an increased risk for PACG by 48 folds (95% CI 8.3, 277.99).

CONCLUSION

Modification of lifestyle may reduce the risk of PACG in Malays. Avoidance of the smoking environment and increase physical activity may prevent the development of PACG in susceptible individual.

CHAPTER 1:

INTRODUCTION

1.1 Primary Angle Closure

Glaucoma is generally identified as a group of conditions resulting in optic neuropathy with characteristic structural damage with specific visual field defect (Foster, 2002). Glaucoma can be classified into two main groups; closed angle glaucoma and open angle glaucoma. Both open and closed angle glaucoma has been further classified into primary or secondary glaucoma (Foster, 2002).

There is confusion regarding the definition of primary angle closure glaucoma (PACG). The latest widely accepted definition of glaucoma is based on International Societal Geographical and Epidemiology Ophthalmology (ISGEO) (Foster, 2002). PACG is defined as primary angle closure (PAC) with evidence of glaucomatous neuropathy. Glaucomatous neuropathy is characterised by structural features exceeding the specified limits for the population, combined with field defect that meets the criteria indicating glaucomatous functional damage. The structural damage include increased vertical cup:disc ratio (CDR) or CDR asymmetry above the 97.5th percentile of the normal population, which indicate glaucomatous loss of the neuroretinal rim. The characteristic visual field defects indicating glaucomatous functional damage include asymmetry across the horizontal midline in early and moderate glaucoma cases, defects located in the mid-periphery in early and moderate cases and defects clustered in neighbouring test points. These visual field defects should be reproducible on at least two occasions and not explained by any other disease. The visual field defects observed should also

be a valid representation of the subjects' functional status based on performance indices, such as false positive rate. Other functional loss indicators include glaucoma hemifield test graded "outside normal limit" and a cluster of three contiguous points at the 5% level on the deviation plot, using the threshold test strategy with the 24-2 test pattern of the Zeiss-Humphrey field analyser (Foster, 2002).

PAC is a condition which describe an eye with occludable angle and features indicating that obstruction to aqueous humor by the peripheral iris has occurred. The features include peripheral anterior synechiae, elevated intraocular pressure, distortion of the radially orientated iris fibres or also known as iris whorling, glaucomfleken lens opacities, or excessive pigment deposition on the trabecular surface. In contrast to PACG, the optic disc in PAC does not have glaucomatous damage (Foster, 2002). The changes in the iridocorneal angle are visible through gonioscopic examination (Bruno and Alward, 2002). PAC can be further classified as synechial closure in which the iridotrabecular contact occur permanently or appositional closure in which the iridotrabecular contact occur intermittently (*World Glaucoma Association. Third Consensus Meeting: Angle Closure Glaucoma, 2006*).

1.2 Prevalence of PACG

Glaucoma is the second leading cause of blindness worldwide. Asians account for approximately half of the world blindness due to glaucoma (Quigley and Broman, 2006). There are currently estimated 60.5 million people with primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG) as of 2010, and projected to be increasing to 79.6 million by 2020 (Quigley and Broman, 2006).

By 2020, it is estimated that bilateral blindness will be present in 5.9 million people with POAG and 5.3 million people with PACG. Asians will represent 87% of those with PACG (Quigley and Broman, 2006). The number of patient affected by glaucoma is projected to be further increasing to 111.8 million in 2040 (Tham *et al.*, 2014).

Asians are a heterogenous multi-ethnic population. There are abundant studies on this ocular disease among Chinese, (He *et al.*, 2006; Jin *et al.*, 2015; Ko *et al.*, 2015) Japanese (Ho *et al.*, 2015; Mizoguchi *et al.*, 2015) and Indian (Duvesh *et al.*, 2013; Kavitha *et al.*, 2014; Sihota, 2011) population. However, there is limited knowledge of PACG on Malay population.

There are racial variations in the manifestation of PACG in different ethnic group due to differences in anterior chamber depth and its association with

peripheral anterior synechiae (Yip and Foster, 2006). In contrast to the pattern of the disease in Caucasians, PACG has a relatively higher prevalence and tends to be asymptomatic in East Asians (He *et al.*, 2006). Compared to eyes with previous history of symptomatic angle closure, asymptomatic PACG was noted to carry poorer visual outcome as they usually present with severe to end-stage visual field loss at first presentation to hospital. It was also noted that the level of presenting intra-ocular pressure (IOP) were not correlated with the visual field outcome (Ang *et al.*, 2004).

Regardless, a long-term outcome of an eye with previous history of acute primary angle closure was also noted to be grave among East Asians. A study conducted in National University Hospital, Singapore and Singapore National Eye Centre involving 90 individuals over the period of 4 to 10 years had shown that after several years of the acute attack, 17.8% were blind in the attacked eye, and almost half had glaucomatous nerve damage (Aung *et al.*, 2004). Understanding the clinical presentation of PACG in Malays are important for part of the formulation for prevention of blindness in Asian population.

In Malaysia, 1.8% of bilateral blindness and 1.8% of low vision was attributed to glaucoma (Zainal *et al.*, 2002). In a study involving 159 respondents aged 40 and above from a rural population in Selangor, Malaysia, the prevalence of glaucoma was reported to be 4.4% (Reddy *et al.*, 2004). Another study involving the urban population in Kuala Lumpur Federal Territory and Klang

Valley at University of Malaya Medical Centre showed that 23.4% of the population were affected by glaucoma, and angle closure glaucoma specifically affected 5% of the population (Reddy *et al.*, 2008). At present, there is no specific population based study conducted among Malays residing in Malaysia.

According to the Singapore Malay Eye Studies (SiMES), a population based study in Singapore involving 3280 participants aged 40 to 80 years, 150 (4.6%) was found to have glaucoma. Based on the study, the age and sex-standardized prevalence for POAG was 2.5%, PACG 0.12% and secondary glaucoma 0.61%. Out of the 150 glaucoma cases, only 12 (8%) had a previous known history of glaucoma, 27 (18%) eyes had low vision and 15 (10%) were blind. Although the proportion of glaucoma attributed to POAG is higher than PACG (69.3% vs. 5.3%), the proportion of people with blindness caused by glaucoma was noted to be higher in PACG (25%) compared to POAG (5.8%) (Shen *et al.*, 2008) Another study in Singapore had shown that the rate of admission for acute, symptomatic angle-closure among Malays was half that of the Chinese population (Wong *et al.*, 2000). However, this may not represent the true incidence in Malays as Malays are minority and constitute only 13.4% of Singapore population (*Population Trends 2016*).

Another retrospective study in Malays residing in Malaysia found that PACG is not uncommon among Malays. Alarmingly, quite a high prevalence of them presented at the late stage of the disease (Liza-Sharmini *et al.*, 2014b). On the

comparison with the presentation of Malaysian Chinese, the clinical presentation is almost similar, but there is significant percentage of Malays who presented at advanced stage and progress faster (Liza-Sharmini *et al.*, 2014a).

1.3 Risk factors for PACG

Several factors had been identified to be significantly associated with increased risk for PACG (Amerasinghe and Aung, 2008) (Amerasinghe *et al.*, 2011) (Kim *et al.*, 2012) (Nongpiur *et al.*, 2011). Owing to the natural pathophysiology of PACG which involve crowding of the angle, ocular biometrical factors had been shown to play a major role in the development of the disease. The biometrical factors involved are shorter axial length of the globe (Kim *et al.*, 2012), shallow anterior chamber depth (Amerasinghe *et al.*, 2011) (Kim *et al.*, 2012), increased iris thickness (Wang *et al.*, 2011) and anteriorly positioned lens (Nongpiur *et al.*, 2011).

In eyes with angle closure, a thicker peripheral iris would be in closer proximity to the angle. With increasing age, the lens thickness increases and results in further shallowing of anterior chamber. In such eyes, iris thickness becomes an important risk factor for the development of angle closure glaucoma (Wang *et al.*, 2011).

With increasing age, the lens vault will also increase due to changes in zonular laxity. This lens vault increment led to higher amount of iridotrabecular contact due to the bulk of the lens anterior to the plane of scleral spur which pushes against the trabecular meshwork; resulting in a more pronounced iris curvature, pupil block, and angle crowding; which contribute to the development of angle closure (Nongpiur *et al.*, 2011). In view of the role played by lens in the mechanism leading to angle closure, surgical lens extraction had been proposed as an alternative approach for the management of angle closure glaucoma (Azuara-Blanco *et al.*, 2016).

Other factors that are associated with higher risk for PACG include female gender, increasing age, and Inuit or East Asian ethnicity (Amerasinghe and Aung, 2008) (Foster, 2002). The higher risk of angle closure in female is possibly related to the anatomical differences compared to males, as females are noted to have shorter anterior chamber depth as well as shorter axial length; both of which are biometrical risk factors for angle closure (Kim *et al.*, 2012). The lens vault was also noted to be greater in female (Nongpiur *et al.*, 2011).

Genetic factors had also been linked to the disease (Vithana *et al.*, 2012) (Khor *et al.*, 2016) (Amerasinghe and Aung, 2008). A study among siblings of Chinese PAC or PACG patients had found that there is a high heritability of narrow angle of almost 60% and their first degree relatives are 7 times more likely to have narrow angles compared to general population (Amerasinghe *et al.*, 2011). A genome-wide association analyses had identified association of

PACG to the loci rs11024102 in PLEKHA7, rs3753841 in COL11A1 and rs1015213 located between PCMTD1 and ST18 on chromosome 8q (Vithana *et al.*, 2012). It was found that there is lack of association between these 3 loci to axial length and anterior chamber depth, which suggest that the predilection to PACG may be mediated by factors other than shallow anterior chamber or length of the globe (Nongpiur *et al.*, 2013). Another genome-wide association study had identified other newer loci that were found to be associated with PACG, including rs3816415 at EPDR, rs1258267 at CHAT, rs736893 at GLIS3, rs7494379 at FERMT2 and rs3739821 located between DPM2 and FAM102A (Khor *et al.*, 2016).

At present, the only modifiable risk factor for glaucoma is IOP and this is applicable to PACG cases too. Higher level of IOP were associated with faster rate of RNFL loss over time (Diniz-Filho *et al.*, 2016). A study looking at continuous IOP monitoring using contact lens sensor had found that the variation in IOP fluctuation is larger in patients with progressive PACG compared to those with stable PACG (Tan *et al.*, 2015). Thus, reduction of IOP is still the mainstay of treatment modalities for glaucoma and this is achieved by means of laser treatment, surgical treatment or medical therapy (Liang *et al.*, 2015) (Ozyol *et al.*, 2016) (Baskaran *et al.*, 2009). Identification of modifiable risk factors other than IOP may provide additional therapeutic targets that would be valuable in the management of patients, particularly those who continue to show substantial progression despite significant lowering of IOP.

Despite extensive studies as described above, the identified risk factors for PACG are mostly non-modifiable. It is important to identify any candidate modifiable factors associated to PACG to be incorporated as part of management for prevention of blindness particularly in Asian region. At present, there are very limited number of studies that look into potential modifiable factor that may affect PACG development. Existing studies on modifiable factors focus more on lifestyle interventions in POAG (Giaconi *et al.*, 2012) (Coleman *et al.*, 2008) (Garcia-Medina *et al.*, 2015) (Jabbarpoor Bonyadi *et al.*, 2014). Lifestyle as a factors that might alter intraocular pressure was also starting to gain attention (Baskaran *et al.*, 2006) (Prata *et al.*, 2010).

Oxidative damage had been proposed as the potential pathogenesis of glaucoma. This postulation is supported by higher concentration of oxidative stress markers such as malondialdehyde (MDA) level, paraoxonase1 (PON1) activity, 8-hydroxy 2-deoxyguanosine (8-OHdG) level and glutathione peroxidase (GPx) activity in glaucoma patients compared to controls (Goyal *et al.*, 2014) (Mumcu *et al.*, 2016) (Ferreira *et al.*, 2004) (Majsterek *et al.*, 2011). Although most studies focused more on POAG, a higher level of oxidative stress was also observed on PACG (Abu-Amero *et al.*, 2014) (Mousa *et al.*, 2015) (Goyal *et al.*, 2014). The levels of vitamin C and vitamin E were also lower in aqueous humor of both POAG and PACG patients compared to cataract patients (Goyal *et al.*, 2014). Thus, potential increase in anti-oxidant intake may provide protective effect against glaucoma (Ramdas *et al.*, 2012).

Higher intake of certain fruits and vegetables high in Vitamin A, Vitamin C and carotenoids, which are all antioxidants, was noted to be associated with lower risk for glaucoma (Giaconi *et al.*, 2012) (Coleman *et al.*, 2008). However, although certain food supplementations may be beneficial to POAG patients, at present, the evidence is not strong enough to support diet changes as part of glaucoma treatment in general (Garcia-Medina *et al.*, 2015) (Jabbarpoor Bonyadi *et al.*, 2014).

Another possible pathogenesis of glaucomatous damage is due to ocular pulse amplitude. It is defined as the difference between diastolic and systolic intraocular pressure. This ocular pulse is generated by the pulsatile ocular blood flow in the choroid. The ocular pulse amplitude in healthy subjects is between 1.2 and 4mmHg. In patients with POAG and NTG, the ocular blood flow regulation was noted to be impaired (Abegao Pinto *et al.*, 2014; Ulrich *et al.*, 2015). However, the association between ocular pulse amplitude or ocular blood flow and PACG had not been studied.

1.4 Effect of cigarette smoking on PACG

Cigarette is known to contain noxious substances that elevate oxidative stress parameters (Carnevale *et al.*, 2016; Rahman and MacNee, 1999). The increased oxidant burden occurs due to presence of free radicals which can generate H₂O₂ by Fenton reaction and are relatively long-lived (Pryor and Stone, 1993). It was found that the level of soluble NOX₂-derived peptide and

8-iso-prostaglandin F₂ α increases with smoking (Carnevale *et al.*, 2016). There is also a significant reduction of nitric oxide bioavailability and vitamin E level (Carnevale *et al.*, 2016).

In view of the recent evidences pointing towards role of oxidative damage in development of glaucoma, more studies are being conducted to look into cigarette smoking as a potential risk factor for glaucoma. However, at present, most of the studies are conducted among POAG patient and the result had not been conclusive (Jain *et al.*, 2016; Zhou *et al.*, 2016). A prospective cohort study among African-American women had found that the incident of POAG is 2 times higher in women who smoke more than 15 cigarette per day and those with more than 20 pack years of smoking compared to those who do not smoke (Wise *et al.*, 2011). Inflammation and apoptosis marker levels measured by means of enzyme immunoassay and western blot procedures were noted to be increasing with smoking in the aqueous humor and plasma samples of women with POAG, which suggest that smoking could be an additional risk factor for progression of glaucoma in elderly women (Zanon-Moreno *et al.*, 2009). A multicentre cross-sectional study conducted at 8 Canadian centers had found that among POAG patients, smoking had been identified as a risk factor for an advanced disease (Buys *et al.*, 2012).

Meanwhile, another prospective study involving 3939 residents aged 55 or older in the Netherland found no clear association between POAG and smoking (Ramdas *et al.*, 2011). A retrospective study involving 7789 Latinos aged 40 and older in California had found that current smokers appeared to

have a lower risk for POAG. However, the apparent protective advantage could not be confirmed as the study had also found that there were lack of association between the number of years since smoking cessation with POAG (Doshi *et al.*, 2008).

Cigarette smoking was also noted to affect vascular integrity (Toda and Toda, 2010) (Powell, 1998). Flow-mediated dilation is a phenomenon in which the vessel dilates when blood flow increases through the vessel, and this requires an intact endothelium of the vessels. This flow-mediated dilation is noted to be decreasing after smoking, indicating endothelial damage to the vascular wall (Carnevale *et al.*, 2016). However, so far, there is no significant difference found in ocular pulse amplitude, retinal thickness and choroidal thickness between smokers and non-smokers (Ulas *et al.*, 2014).

Cigarette smoking may also be related to glaucoma due to its effect on the intraocular pressure, which is a significant risk factor for glaucoma. An earlier study that lead to investigation of association between intraocular pressure and glaucoma is findings from the Blue Mountain Eye Study, which suggested that smoking may cause elevation of IOP. Current smokers were found to have slightly higher mean IOP compared to control subjects (Lee *et al.*, 2003). Closer to Malaysia, a study on Japanese population had also found that IOP is affected by smoking habit (Yoshida *et al.*, 2014). On the contrary, The Rotterdam study found that there is no significant association between cigarette smoking and IOP (Ramdas *et al.*, 2011). The role of cigarette in IOP is still debatable.

A retrospective record review involving 662 PACG patients found that the risk of PACG among smoker was increased by 0.515 (95% CI 0.293 – 0.906, $p < 0.05$) (Zhao Y et al, 2015). There is no other study looking into the potential effect of cigarette smoking in PACG.

1.5 Effect of physical activities on PACG

Physical activity is defined as any bodily movement produced by skeletal muscles that require energy expenditure. This include not only exercise, but also other activities involving bodily movements which are done as part of playing, working, active transportation, house chores and recreational activities. The intensity of physical activities are frequently expressed as Metabolic Equivalent (METs). One MET is defined as the energy cost of sitting quietly and is equivalent to a caloric consumption of 1kcal/kg/hour. Caloric consumption is estimated to be three to six times higher when being moderately active (3-6 METs) and more than six times higher when being vigorously active (>6 METs) in comparison to sitting quietly. A moderate-intensity activity are activities that requires a moderate amount of effort and noticeably accelerates the heart rate, whilst vigorous-intensity physical activities are activities that requires a large amount of effort and causes rapid breathing and a substantial increase in heart rate (WHO, 2016). Gardening, doing housework and domestic chores and carrying moderate loads weighing less than 20kg are the example of moderate-intensity physical activities.

Running, fast cycling, heavy shovelling and carrying loads weighing more than 20kg are among the example of vigorous-intensity physical activities.

The exact mechanism on the effect of exercise on IOP is not completely understood. The understanding on this subject had been limited despite numerous studies due to the heterogeneity of the studies conducted, which include the study parameters, exercise protocol and IOP measurement (Roddy *et al.*, 2014). For example, exercises involving Valsalva manoeuver had been shown to increase IOP (Vieira *et al.*, 2006). Heavy weight lifting had been also shown to cause IOP elevation (Risner *et al.*, 2009). However, on the contrary, exercise bike was found to cause IOP reduction (Saarela *et al.*, 2013).

Physical fitness had been associated with lower baseline IOP but diminished acute IOP-lowering response to exercise. Meanwhile, glaucoma patients demonstrate greater IOP lowering effect compared to healthy subjects. In healthy subjects, the ocular blood flow remains unchanged during exercise due to vascular autoregulation (Risner *et al.*, 2009). In glaucoma, preventing a large IOP fluctuation may be as important as attaining a target IOP in preventing glaucoma progression ("The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators," 2000).

The effect of physical activity on PACG had not been previously investigated. Dynamic iris changes had been shown to play a role in the pathogenesis of

primary angle closure (Zhang *et al.*, 2016). The dynamic iris changes that occurs during exercise may or may not show any effect in the development of PACG, but there are no studies conducted to look into the aspect.

1.6 Rationale of study

Glaucoma is a chronic disease with progressive optic neuropathy that requires a lifelong treatment and follow-up. It causes financial burden in health care budget. Based on the Ministry of Health, Malaysia, 70% to 80% budget allocated to pharmacy of eye care is spent on glaucoma treatment (*Clinical Practice Guideline: Management of Primary Open Angle Glaucoma*, 2008).

PACG subjects are chosen as there are not many studies related to lifestyle modification among PACG being conducted worldwide. Besides, PACG was noted to carry a significant burden to the Asian population (Tham *et al.*, 2014) (Quigley and Broman, 2006). This study is designed to look at cigarette smoking and physical activities as they are modifiable factors and previous studies had shown potential link between these two aspects and oxidative damage, alteration of IOP, or alteration of ocular perfusion; which are related to the pathogenesis of glaucoma.

The famous quote; ‘prevention is better than cure’, is also applicable to glaucoma. Identification of the potential modifiable risk factor is important especially among susceptible individuals, and give them the sense of

empowerment to alter their lifestyle to reduce the risk of developing glaucoma. Subsequently, it will also be of economic benefit for preventive measures and reduce the cost of treating the disease when it has already progressed.

1.7 Malay Glaucoma Eye Studies (MaGES)

Malay Glaucoma Eye Study is a multicentre study, designed to assess the risk factors for primary glaucoma among Malays in Malaysia. It looked into the aspect of genetic, dietary, physical activities and cigarette smoking as a potential modifiable factor for primary glaucoma.

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