

**EVALUATION OF SEXUAL DYSFUNCTION AND  
ITS ASSOCIATED FACTORS IN PRIMARY OPEN  
ANGLE GLAUCOMA PATIENTS**

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**DISCLAIMER**

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

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## **ABSTRAK**

### **PENDAHULUAN**

Malaysia dijangka akan menjadi sebuah negara tua pada tahun 2030. Disfungsi seksual dan glaukoma sudut terbuka primer merupakan penyakit yang umumnya ditemui dalam kalangan populasi tua dan prevalens meningkat mengikut umur. Tambahan lagi, jangka hayat manusia telah meningkat. Glaukoma sudut terbuka primer merupakan jenis glaukoma yang paling lazim dan dikenali sebagai 'pembunuh diam visi'. Disfungsi seksual mempengaruhi kualiti hidup ditambah lagi bebanan dari penyakit glaukoma. Justeru itu, pertimbangan dalam menempuh kehidupan waktu tua adalah penting untuk masa hadapan bagi mencapai kesejahteraan hidup.

### **OBJEKTIF**

Tujuan kajian ini adalah untuk menilai disfungsi seksual dan faktor-faktor yang mempengaruhinya di antara pesakit glaukoma sudut terbuka primer.

### **KAEDAH KAJIAN**

Satu kajian rentas telah dijalankan yang melibatkan pesakit glaukoma sudut terbuka primer di antara September 2019 dan September 2020 di klinik oftalmologi di Malaysia: Hospital Raja Permaisuri Bainun (HRPB), Hospital Raja Perempuan Zainnab II (HRPZ II) dan Hospital Universiti Sains Malaysia. Hanya subjek yang dalam lingkungan umur 40-80 tahun yang menghadiri klinik dan dapat melakukan ujian medan penglihatan menggunakan analisis Humphrey visual field 24-2 yang tepat sekurang-kurangnya dua kali secara berulang, akan dipilih. Subjek ditemuduga mengenai data demografi dan info kesihatan terkini. Tahap keterukan glaukoma adalah berdasarkan sistem skala 'Advanced Glaucoma Intervention Study' (AGIS) yang telah dimodifikasi. Tahap keterukan glaukoma terbahagi kepada ringan, sederhana dan teruk. Penilaian subjek

berisiko disfungsi seksual dibuat berdasarkan borong soal kaji selidik yang telah divalidasi: 'International Index of Erectile dysfunction' (IIEF-5) untuk subjek lelaki dan 'Female Sexual Function Index' (FSFI-6) untuk subjek wanita.

## **KEPUTUSAN**

Seramai 432 subjek yang mempunyai penyakit glaukoma sudut terbuka primer telah menyertai kajian ini (222 lelaki dan 210 wanita). Dua kumpulan dinilai dan dianalisa dengan menggunakan borong soal selidik berlainan. Prevalens untuk disfungsi erektil adalah setinggi 91% dalam kalangan lelaki dengan menggunakan soal kaji selidik IIEF-5 dan 78.5% dalam kalangan wanita dengan menggunakan soal kaji selidik FSFI-6. Prevalens disfungsi seksual didapati meningkat mengikut umur. Terdapat hubungan yang signifikan di antara disfungsi erektil dan tahap keterukan penyakit glaucoma ( $p < 0.001$ ) manakala tidak ada hubungan di antara disfungsi seksual dan tahap keterukan glaucoma dalam kalangan wanita. Wanita yang mempunyai tahap pendidikan yang tinggi didapati 67% rendah nisbah odds untuk mengalami disfungsi seksual (95% selang keyakinan = 0.12, 0.88). Umur merupakan faktor yang mempengaruhi disfungsi erektil dalam kalangan lelaki (OR = 1.23, 95% CI = 1.10, 1.38).

## **KESIMPULAN**

Prevalens disfungsi seksual adalah tinggi di kalangan pesakit glaukoma sudut terbuka primer. Isu seksual di kalangan orang tua patut dititik berat memandangkan Malaysia dijangka akan menjadi negara tua pada tahun 2030. Hubungan seksual dalam kalangan populasi tua merupakan salah satu elemen yang penting dalam kehidupan dan berhubung kait dengan kualiti hidup.

## **ABSTRACT**

### **INTRODUCTION**

Malaysia is expected to be an aging nation by 2030. Sexual dysfunction (SD) and primary open angle glaucoma (POAG) are diseases that generally affect older population. The prevalence of both diseases is increase with age. Moreover, human life expectancy increases over time. POAG is the most common form of glaucoma and is known as 'silent thief of sight'. SD affects quality of life on top with the treatment burden from POAG. Thus, consideration to confront the older adults is important to warrant an individual's future well-being.

### **OBJECTIVE**

The aim of this study is to evaluate sexual dysfunction (SD) and its associated factors in primary open angle glaucoma patients.

### **METHODOLOGY**

A cross sectional study was conducted from September 2019 to September 2020 involving three ophthalmology clinics in Malaysia: Hospital Raja Permaisuri Bainun (HRPB), Hospital Raja Perempuan Zainnab II (HRPZ II) dan Hospital Universiti Sains Malaysia. Only participants aged between 40-80 years old who attended clinic and able to provide two consecutive reliable and reproducible Humphrey visual fields (HVF) 24-2 were recruited. Participants were interviewed on demographic data and latest health status. Severity of glaucoma was based on modified Advanced Glaucoma Intervention Study (AGIS) scoring system on HVF and categorized into mild, moderate and severe glaucoma. SD assessment was done using validated Bahasa Malaysia version of

'International Index of Sexual Function' (IIEF-5) for male POAG participants and 'Female Sexual Function Index' (FSFI-6) for female POAG participants.

## **RESULT**

A total of 432 participants with pre-existing POAG were recruited (222 men and 210 women). Men and women were assessed and analyzed differently by using two different questionnaires. Prevalence for erectile dysfunction (ED) was 91% by using IIEF-5 questionnaire and prevalence rate of female sexual dysfunction (FSD) was 78.5% by using FSFI-6 questionnaire. Prevalence of ED and FSD increased with age. There was significant association between ED and severity of glaucoma ( $p < 0.001$ ) but not found in FSD. High educational level had 67% lower odds to experience FSD compared to lower educational level (OR=0.33, 95% CI=0.12, 0.88). For 1 year older in male POAG patients, there were 1.23 times odds to experience ED (OR=1.23, 95% CI=1.10, 1.38).

## **CONCLUSION**

Prevalence of SD is high in patients with POAG in our study population. Malaysia is expected to be aging nation by 2030. Sexual health in older adults should not be overlooked as both diseases are affecting them. Sexual health is an integral part of overall health in older life and quality of life includes the pleasure of sexual activity.

# **CHAPTER 1-**

# **INTRODUCTION**

## **1.1 Primary Open Angle Glaucoma**

Primary open angle glaucoma (POAG) is a chronic disease with progressive optic neuropathy, characterized by morphological changes of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL) with corresponding visual field (VF) defect (European Glaucoma society 2014). POAG is relatively asymptomatic, especially in early stages, which lead to late diagnosis. In addition, poor public awareness of glaucoma and its risk factor further compromised the situation (Maier et al., 2005). It is often described as "silent thief of sight", which cause a bilateral, painless progressive loss of vision.

POAG is defined as 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 suggested by 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 provides 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 important for monitoring of function decline and progression in glaucoma (World Glaucoma Association 10th Consensus, April 2016).

### **1.1.1 Global Prevalence of POAG**

World Health Organization (WHO) in 2002 demonstrated that 37 million people were blind worldwide (Kingman S, 2004). Estimation of 8.4 million people were blind secondary to glaucoma and the number is 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 and the estimation of prevalence of POAG escalated to 66.8 million people worldwide.

Based on a systemic review and meta-analysis, the overall global prevalence of glaucoma was 3.54% with POAG contribute 3.05% (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 have 1.36 folds risk (95% CI, 1.23-1.52) to develop POAG compared to women (Tham et al., 2014). It 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).

### **1.1.2 Prevalence of POAG in Asia**

POAG is the second leading cause of blindness in the world (Quigley and Broman, 2006). Systemic review and meta-analysis established that POAG was the predominant glaucoma subtype in Asia, particularly affecting East and South-Central Asia regions (Chan et al., 2016; Tham et al., 2014). Being the most common glaucoma subtype in Asia, the prevalence of POAG varies from different part in Asia. In South East Asia, the prevalence rate of POAG was ranged from 2.0% to 2.5% (Shen SY et al., 2008; Casson RJ, 2007). China reported prevalence rate of 0.7%-2.8% in different districts (He JN et al., 2015, Liang YB et al., 2011, Sun J et al., 2012). In South Korea, the

prevalence rate of POAG was reported higher, ranged from 3.5% to 4.9% (Kim CS et al., 2011; Kim KE et al., 2016). Similar prevalence rate of 3.9% was reported in Japan (Iwase A et al., 2004).

## **1.2 Glaucoma Progression and Severity**

POAG is a progressive disease, structural and functional changes occur slowly but faster than natural aging process. Assessment of the severity of POAG is important for personalization and optimization of treatment. Detecting the presence of visual field (VF) progression is a crucial in the management of glaucoma, affecting the decision to initiate, intensify or advance therapy. Standard automated perimetry (SAP) remains the method of choice for monitoring functional changes in glaucoma. Various studies have used VF outcome as an end point (Scuderi et al., 2008; Alencar and Medeiros, 2011; Sethi S, 2013) to detect progression. The evaluation of VF progression can be achieved by employing trend-based analysis and event-based analysis (Spry and Johnson, 2002; Casas-Llera P et al., 2009).

### **1.2.1 Evaluation of Visual Field Progression**

#### **1.2.1.1 Trend- based Analysis**

Trend-based analysis uses mean deviation index (MDI) or visual field index (VFI) calculated from the Humphrey visual field (HVF) perimetry. It has become a standard index for clinicians to estimate the progression rate of glaucoma (Casas-Llera P et al., 2009). However, it has limitations as MDI can be influenced by the presence of cataract or opacity correlate poorly with clinical findings. Thus, it may give rise to false positive high glaucoma progression rate (Koucheiki et al., 2004). The value of MDI will improve after cataract extraction and this may delay the evaluation glaucoma progression and treatment (Koucheiki et al., 2004). Another limitation of using MDI is



that it is very weakly centre weighted; therefore it does not correlate well to patient's real visual function (Heijl et al., 1986).

### **1.2.1. 2 Event-based Analysis**

The event-based analysis is essential to detect whether progression presence or not (Rao HL, 2013). AGIS (Advanced Glaucoma Intervention Study) investigators developed scoring system; 0 (no defect) to 20 (all test sites deeply depressed). Visual field considered progress if there is a worsening of 4 units in the AGIS score sustained during 3 consecutive 6-month visits (Investigators, 1994). Another staging system was proposed by Mills RP by upgrading Hodapp-Parish Anderson criteria (Mills et al., 2006). There are three factors on categorizing of stages; stages 0 and 1 depends on pattern standard deviation (PSD) and hemi field test results, 9 stages 2 through 4 are adjusted by numeric (dB) plot, and the pattern deviation plot is used for 1 through 4. Stage 5 classifications are on the basis of poor visual acuity and inability to perform VF testing as a result of a severe loss of vision. Progression was considered when VF progress from one stage to the next (Mills et al., 2006). Glaucoma progression analysis (GPA) software incorporated in Humphrey Visual Field Analyzer (HVA) (Carl-Zeiss Meditec, Dublin, CA) is an example of event-based analysis (Casas-Llera et al., 2009). The software will give an analysis of pattern standard deviation values (Casas-Llera et al., 2009) allowing for glaucoma progression monitoring. Recently, glaucoma progression index (GPI) was introduced to measure the rate of VF progression (Bengtsson et al., 2009). It was found that GPI analysis is more accurate than the traditional MDI analysis for determining the rate of progression and is considerably less affected by cataract or cataract surgery (Bengtsson and Heijl, 2008). The event-based GPA analysis is capable of detecting progression earlier compared to trend VFI analysis by 7 months (Casas-Llera et al., 2009). An innovative study combining both

Medeiros and colleagues in which it shows promising reliability in measuring visual field progression outcome (Casas-Llera et al., 2009).

### **1.2.2 Staging and Severity of Glaucoma**

Standardization of glaucoma severity scoring is important 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 severe or end staged based on structural damage and extension of the VF defects (Susanna Jr. and Vessani, 2009).

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

#### **1.1.2.1 Hodapp-Parish-Anderson (HPA) Classification**

Hodapp, Parish and Anderson (H-P-A) classification is based on two criteria; the first criterion looking to the extent of damage, using MDI value and the number of defective points in Humphrey Statpac-2 pattern deviation probability map of the 24-2 SITA STANDARD 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).

### **1.2.2.2 Advanced Glaucoma Intervention Study (AGIS)**

A continuous glaucoma staging systems have been recommended by investigators in the Advanced Glaucoma Intervention Study. In this scoring system, the severity of glaucoma is 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. This is an event-based analysis (Investigators AGIS, 1994; Ng et al, 2012). The scores for each hemi field and nasal area are summed up and visual field scores are divided into five 11 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 provides 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).

### **1.3 Sexual Dysfunction**

WHO has defined sexual health as a "state of physical, emotional, mental and social well-being related to sexuality, not merely the absence of disease dysfunction or infirmity?" Satisfaction with sexual life has been shown to be an important predictor of life satisfaction as a whole (Fugl-Meyer AR et al., 1997). Quality of life (QoL) include the pleasure of sexual activity (Spatz ES et al., 2013, Lindau ST et al., 2007, Patel D et al., 2003, Diener E and Chan MY, 2011, Flynn TJ and Gow AJ, 2015, Heiman JR et al., 2011). Several studies have suggested that those who engage in sexual intercourse were likely to have a better quality of intimate relationships, higher self-esteem and lesser depressive symptoms (Brody S, 2010, Choi K, 2011). Sexual activity is associated with benefits for psychological and physiological well-being, such as improved QoL and

mental health, increased heart rate variability, and lower risk of certain cancers and fatal coronary events (Brody S, 2003, Costa RM, 2012, Ebrahim S et al., 2002)

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) categorized sexual disorders into four major groups: Sexual dysfunction (SD), Paraphilia, Gender identity disorders and sexual disorder not otherwise specified. Sexual dysfunction is used to code the problems in sexual desire or psychophysiological changes in the sexual response cycle. Paraphilias are characterized by recurrent, intense sexual urges that involve unusual objects or activities. Gender identity disorders involve persistent cross-gender identification and discomfort with one's assigned sex. Sexual disorders not otherwise specified are used to code disorders that are not fit into any categories.

SD is characterized by persistent problems with sexual response or pleasure despite in the presence of adequate stimulation, cause significant distress and interpersonal strain. The American Psychiatric Association's (2013) Diagnostic and Statistical Manual of Mental Disorders, *Fifth Edition* (DSM-5) describes total ten subtype of sexual dysfunctions (4 subtypes for male; 3 subtypes for female; 3 subtype for both male and female: delayed ejaculation, erectile disorder, male hypoactive sexual desire disorder, premature ejaculation, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, substance/medication-induced SD, other specified sexual dysfunction, and unspecified sexual dysfunction.

SD can be divided into primary and secondary SD. It is call primary SD when the person has never experienced sexual satisfaction. It may be caused by underlying developmental disorders of the neurological, endocrine, urogenital and other psychiatric cause. Secondary SD is in which former enjoyment of sexual activity is no

longer present. It is more likely to result from an acquired systemic disorder such as cardiovascular disease, diabetes mellitus, obesity, depression, or anxiety.

Potential impact of sexual disorders on interpersonal relationships and epidemiological data are relatively scarce. SD is associated with psychosocial problems such as low self-esteem, depression, anxiety, relationship or marital problems (Althof, 2002). Erectile dysfunction (ED) has a significant negative impact on the QoL of affected individuals and their partner (Althof, 2002). Moreover, it was found that men with both ED and medical comorbidities have poorer QoL as compared to those without illness (Rosen et al., 2004).

Sexual disorder is considered as a social taboo that sometimes imposes dangerous threat to most of Asian societies. This is considered as the pride for both men and women. Asians are tending to consider and accept sexual dysfunctions as a part of the normal aging process due to different culture and religious beliefs (Ho CC et al., 2011). Health-seeking behaviour implies a loss of status and control, and may damage their identity (Yates M et al., 2008). Thus, men tend to not address their sexual problems because they fear loss of control and loss of their cultural role (Bhui K et al., 2002). Low WY et al. reported that Chinese men are not likely to disclose their sexual dysfunctions despite have a lower QoL with family life or work life, intimate relationship and general happiness. When topic of SD is culturally restricted, and accessibility to health care in developing countries is an issue, alternative medication is preferable choice in view of Asia is blessed with many types of traditional medications and the price is more affordable. In Malaysia, up to 65% of men felt that traditional medications are better than conventional treatment. (Low WY and Tham HM, 2007)

### **1.3.1 Prevalence of SD**

Erection dysfunction (ED) is a common sexual problem among men and prevalence increases with age (Haczynski J et al., 2006). A meta-analysis of prevalence of ED in Asia varies in between 9% and 73% (Ho CC et al., 2011). The self-reported prevalence of ED in Malaysia is 26.8% to 69.5% (Asnida Anjang et al., 2011; Low WY et al., 2006; Khoo EM et al., 2008) The prevalence of ED using self-reported questionnaire International Index of Erectile Dysfunction (IIEF-5) reported 69.5% of men aged 40-79 years in primary care clinics in Petaling district, Malaysia, (AsnidaAnjang et al.,2011). The prevalence increases with age: 3.4% to 32.5% in 40-49, 10.4% to 52.4%, in 50-59, 28.0% to 68.5% in 60-69, 41.9% to 69.2% in 70-79 and highest among those above 80 years (76.2%). Longevity seems to play a role in ED, this indicate a close relationship with glaucoma.

Less importance was given to female sexual dysfunction (FSD). The prevalence of FSD is estimated to be 25% to 63%. Women with menopause reported higher prevalence rate of FSD, from 68% to 86.5%. In Malaysia, the prevalence of FSD was reported 29.6% and 25.8% using the Malay Version Female Sexual Function Index (MVFSFI) (Sidi et al., 2007; Ishak et al., 2010). The risk factors include: older age, Malays, duration of marriage of more than 14 years, multiparity, older husband, and higher academic status (Sidi et al., 2007). Systemic diseases such as peripheral vascular or cardiovascular diseases, hypertension and high blood cholesterol levels are also identified as risk factors for FSD (Berman et al., 2002).

Thus, if one have ocular problem with systemic co morbidities and SD, their QoL is further deteriorated. Poor QoL is associated with poor adherence and persistence to treatment, which indirectly causing further progression of glaucoma. Identification of SD is also important to ensure good QoL among elderly. 'Aging gracefully' or 'Healthy aging' should encompass all aspect of life.

Open angle glaucoma patients are more likely to have different co-morbidities that may be life threatening and affect QoL.(Lin et al, 2010). There is a relationship between VF loss and QoL (Mills RP et al, 1998; Jampel HD, 2001). Greater severity of VF abnormality was associated with significantly greater disability with vision-related function and physical function. (Qiu M et al., 2014). Bilateral VF defect are associated with vision-related quality of life deterioration regardless of visual acuity (Rui E et al., 2018)

### **1.3.2 Sexual Dysfunction and Aging**

Sexuality is an aspect of the emotional and physical intimacy that men and women experience throughout their life. Sexuality differs according to gender, and socio-culture, more individualize. Sexuality and responsiveness rate increases is slowly declining with age (Haton K et al., 1994, Mulligan & Moss 1991). Aging causes physiological changes in sexuality of both men and women. Sexual response cycle is divided into four phases: excitement, plateau, orgasm and resolution. Similar sequence of sexual cycle was found between male and female. In general, the sexual response cycle is the same for both men and women but differ in timing as men undergo a refractory period following orgasm, whereas women may capable for multiple orgasm (Masters and Johnson 1970)

Age related changes on sexuality in men and women can be attributed by many factors. Physiologic changes can affect the sexual response of men and women and may inhibit sexual function as people age (Bachmann GA and Avci D, 2004; Rosen, 2005). Sex desire declines in both men and women with age. The factors influence on sex desire include health of the individual and partner, physical and social environment, psychological and emotional feeling, past experiences, relationship with the partner, and hormonal changes (Lindau et al., 2007).

Longer life expectancy and wider emphasized of treatment for SD causes recent rise in interest in sexual problems of older adults. In general, aging reduces sexuality among older adults. Based on random population survey among adults aged between 40 and 80 years old in urban population of Asian countries, the prevalence of sexual activity declined with age (Nicolosi et al, 2005). Among men, sexual intercourse during the past 12 months reduced from 92.6% to 49.4% in those age 40-49 years and 70-80 years respectively. The effect is greater among women compared to men, drastically dropped from 85% at 40-49 years to 18.4% at 70-80 years.

The prevalence of ED is between 3.4% and 32.5% in their forties, 10.4% to 52.4% in their fifties, 28.0% to 68.5% in their sixties, 41.9% to 69.2% in their seventies and above 80 years old the prevalence was 76.2% (Haczynski et al., 2006; Lyngdorf et al., 2004, Che et al., 2000; Cho et al., 2003). In Malaysia, in primary care setting in urban district in Selangor state using IIEF-5 questionnaire, 69.49% of participants have ED and the prevalence increased with age. It was also found that severity of ED increased with age (Asnida Anjang et al, 2011).

Various studies on FSD showed the prevalence varies between 50% and 75% in menopausal women (Beigi M and Fahami F 2012). A comparable prevalence rate of 56% of allied health workers in Singapore tertiary hospital reported to have FSD but recruited subjects are aged from 18 to 70 years (Safdar F et al., 2019). The prevalence of FSD in menopausal women was reported as high as 91.2% in Hong Kong. (Wong EL et al., 2018) However, a local study in Malaysia reported prevalence of FSD in menopausal women only 21.3% (Malini Mat Napes, 2012). Menopause causes decline in sexual desire (Nappi & Lachowsky 2009). A cross sectional study involved married women in Malaysia aged between 18-65 years old found that the prevalence of FSD



increased significantly with age. The prevalence increased from 17.7% in the age group of 31-45 years to 38.8% in age group of 45-65 years (Ishak et al, 2000).

Sexuality issues are a taboo in most population especially in Asia. SD in older adults is difficult to assess, often due to embarrassment on the part of the patient or doctor. In a study examining the attitudes and practices among general practitioners in Malaysia majority of the doctors were reluctant to discuss sexual issues with their patients (Low et al., 2002). The reasons include time constraints, lack of training and knowledge on sexuality, being the opposite sex to their patients, and fear of offending the patients. Likewise, patients especially men considered SD affect their self identity and reluctant to discuss about with it.

### **1.3.3 Sexual Dysfunction and Gender**

Due to the different in anatomy, psychology and emotionally, there is different in SD between men and women. Both male and female sexual response cycle consists of 4 phases: excitement, plateau, orgasm, and resolution. In men, penile erection is essential to initial event. Both men and women begin in the desire phase, which is controlled by a balance of the dopamine-sensitive excitatory center and the serotonin sensitive inhibitory center in the brain (Basson R, 2001). Testosterone is reported to respond to the modulating of the threshold of these centers. Sacral parasympathetic and thoracolumbar sympathetic nerves provide the efferent vasodilator input to the penis which in turn cause arteriolar dilatation and increased blood flow to the erectile tissue of the penis in excitement phase. During plateau phase, parasympathetic nerves stimulate secretion from the seminal vesicles and prostate and Cowper's glands and followed by orgasmic phase, which is characterized by seminal emission and ejaculation and the accompanying sensations. Emission of semen into the urethra is via contractions of smooth muscles in the vas deferens, seminal vesicles, and prostate

which controls by sympathetic nerves. Rhythmic contractions of bulbocavernosus and ischiocavernosus) muscles generated by pudendal nerve eject semen from the urethra.

In female, the parasympathetic nervous system mediates series of genitalia changes and vascular engorgement (enlargement of the clitoris, dilation of perivaginal arterioles, and expansion of the inner two-thirds of the vaginal barrel). Vaginal lubrication regulated by estrogen cause transudation across the vaginal mucosa (Tsui KH et al., 2011). At the plateau phase, the length and width of the inner two-thirds of the vagina expands, and the outer one third of the vagina becomes congested with blood. A series of contractions of the related genital muscle groups occurs at the orgasmic phase associated with elevate heart rate, blood pressure, and respiratory. Women can response to repeated stimulation, and reach second or third orgasm soon after the first without refractory period.

#### **1.3.4 Sexual Dysfunction and Glaucoma**

A cross sectional study using patient questionnaire, involving 167 subjects found significant association between ED and glaucoma (Geoffrey L et al., 2016). There was also positive association between severity of ED and severity of glaucoma (Nathoo et al., 2016). This finding may suggest a common mechanism between open angle glaucoma and ED.

Endothelial dysfunction, in which damage to the lining of the arterial walls impairs the nitric oxide (NO) pathway and vasodilatation, is an important factor underlying both SD and open angle glaucoma (Fukumura D et al., 2001). Glaucoma is a multi-factorial optic neuropathy of unknown aetiology. Elevated IOP is the most important risk factor for the disease. Two other possible mechanisms have been

postulated as causative for POAG which are vascular dysfunction that causes ischaemia in the optic nerve and mechanical dysfunction via compression of the axons.

A few animal and human studies have indicated vascular dysregulation caused by endothelial dysfunction play a role in the pathogenesis of the POAG (Grieshaber MC et al., 2007, Su WW et al., 2008). The vascular endothelium is an important source for the production of NO, which is a potent modulator of vascular tone. NO is involved in the control of basal blood flow in the choroid, optic nerve and retina by maintaining the basal vasodilator tone. Similarly, endothelial dysfunction also had been identified to be involved in pathophysiology of ED and FSD (Burnett Al et al., 1992, Tarcan T et al., 1999)

#### **1.4 Sexual Dysfunction Assessment**

Sexuality has become an important issue of health. Sexual problems are highly prevalence in both genders (Bacon CG et al., 2003, Seftel AD et al., 2003), but is frequently under-recognized in clinical practice (Mercer CH et al., 2003). Sexual function is complex and involves different biospsychological aspects which include biological or organic condition, a psychological condition and or a social condition. Clinical evaluation of sexual function requires thorough and comprehensive medical interview, physical examination, and laboratory investigations that focus on sexual function and psychometric assessment.

Clinicians can screen all patients, regardless of age, face to face during a routine clinic visit. However, a holistic approach to obtain and use the full range of information to direct the diagnostic and therapeutic intervention is rather difficult. A detailed obstetric and gynecologic history and sexual history that includes any sexually transmitted diseases, sexual abuse, urinary and bowel complaints, or surgeries which are another difficult questions to decode. Thus, to overcome their reluctance, there are

many questionnaires for screening SD. Most of the questionnaires are self-administrated or self reported. The accuracy of the diagnosis of SD based on the questionnaire is always an issue. Nevertheless, these questionnaires may help to evaluate certain area of sexual functioning and provide some quantification of SD (Hatzichristou D et al., 2004).

Some of the most commonly used questionnaires to assess ED include International Index of Erectile Function (IIEF), Erection Hardness Score (EHS), and Quality of Erection Questionnaire (QEQ). For female, Female Sexual Function Index (FSFI) and Sexual Function Questionnaire (SFQ) are commonly used to assess FSD.

#### **1.4.1 Sexual dysfunction related questionnaire**

##### **1.4.1.1 International Index of Erectile Function (IIEF)**

The IIEF was developed by Rosen RC in 1997 in several stages, including initially pretesting with selected patient groups and expert panel consultants, followed by intensive validation process. It comprises of five domains: erectile dysfunction, orgasm function, sexual desire, intercourse satisfaction and overall satisfaction. There are a total of 15 questions in this questionnaire. Scale reliability was tested in two different aspects which were internal consistency and test-retest repeatability. Response was found to be satisfactory to highly consistent. Discriminant validity was highly significant between patients with ED and age-matched control; greatest for erectile function domain ( $p < 0.0001$ ). All five domains achieved high degree of sensitivity and specificity to the effect of treatment ( $p < 0.0001$ ).

Five-item short version (IIEF-5) was developed by Rosen RC in 1999 to diagnose the presence and severity of ED. Based on equal misclassification rates of ED and no ED, a cutoff score of 21 discriminated best (sensitivity=0.98, specificity=0.88). IIEF-5 focuses on a single domain: erectile function. There is total of five questions

with each score of 0 to 5 and maximum score of 25. Erectile dysfunction is defined when the score of IIEF-5 is between 5 and 21. It is divided according to severity; mild (17-21), mild to moderate (12-16), moderate (8-11) and severe (5-7). Those score between 22 and 25 is regarded as normal erection. It is best used in older adults due to the short duration to complete the questionnaire and practical in a busy practice.

Cross-cultural adaptation and validation of English version of IIEF for use in Malaysia was done by Lim TO et al. in 2003. The correlation coefficient for the total score was 0.98. Scale reliability for both IIEF 15 and IIEF-5 was high (alpha value of 0.96 and 0.90 respectively). Discriminant validity was found to be good in both IIEF and the IIEF-5. The Malay IIEF was sensitive to treatment response but no report on specificity in view of only 24 subjects were recruited.

#### **1.4.1.2 Female Sexual Dysfunction Index (FSFI)**

FSFI was developed by Rosen RC in 2000 with six-domain structure identified, which included desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. Overall test-retest reliability coefficients were high for each of the domains ( $r = 0.79$  to  $0.86$ ), a high level of internal consistency was observed (Cronbach's alpha values of  $0.82$  and higher) and good construct validity was demonstrated ( $p < \text{or} = 0.001$ ).

The Malay version of FSFI is a validated and locally accepted questionnaire for use in the assessment of FSD in the Malaysian population and was found to have good discriminant validity as a whole and for each domain (Sidi et al., 2007). Total of six domains were assessed and it includes sexual desire disease, sexual arousal disorder, lubrication, orgasmic disorder, sexual dissatisfaction, and sexual pain disorder. It consists of total 19 items. A score of less than 19 indicates some extent of sexual dysfunction.

FSFI-6 is a multi-dimensional self-report test that simplified from FSFI. It comprises of 6 questions that include each domain of FSD. The maximum score for FSFI-6 is 30. FSD is considered and need further evaluation if the score is less than or equal to 19. Using the cut-off of 19, the sensitivity and specificity of the test were, 0.93 and 0.94, respectively. Reliability, internal consistency, and stability on retest were also good (Isidori AM et al, 2010).

## **1.5 Other Factors Affecting Sexual Dysfunction**

### **1.5.1 Diabetes Mellitus**

Diabetes mellitus is one of the most common chronic diseases in nearly all countries and expected to rise to 552 million by 2030 (Wild S et al., 2004). The pathophysiology of ED in diabetes is multifactorial which include vascular and neurologic insults. Penile erection is the result of relaxation of smooth muscle in the cavernous body and associated blood vessels (Dean RC and Lue TF, 2005). Smooth muscle relaxation is mediated primarily by NO which is synthesized from the autonomic postganglionic parasympathetic nerves (Cellek S et al., 2013) and in the endothelium lining the blood vessels and cavernosal sinusoids. Hyperglycemia caused an acute and transient reduction in endothelium-dependent vasodilatation (Loader J et al. 2015) which attributed to increased vasoconstrictor mediators and decreased endothelial NO production.

Reduction of blood flow in the autonomic ganglia causes several neuronal events both in the cell body and axon of the neuron: disturbances in membrane conductivity, impaired nerve conduction and action potential generation, and decreased axonal transport (Cellek S et al., 2013). These events become irreversible in view of ongoing hypoxia and nerve dysfunction and accumulation of advanced glycation end products in diabetes patients.

Diabetes mellitus is associated with ED in men (Maiorino MI et al., 2014) and FSD in women (Esposito K et al., 2010). There was reported a 3-folds probability of having ED among men with diabetics compared to non-diabetic (Feldman HA et al., 1994). Higher prevalence of FSD is found in diabetic women than in non-diabetic women (Pontiroli AE et al., 2013). A meta-analysis showed a higher frequency of FSD in diabetic women than in healthy controls with an odds ratio of 2.27 in type 1 diabetes, 2.49 in type 2 diabetes, and 2.02 when considering any form of diabetes. (Pontiroli, A.E et al., 2013). According to a recent meta-analysis, the overall prevalence of FSD in women type 2 diabetes mellitus was 68.6% (95% CI 61.6–75.3%) (Rahmanian, E et al., 2019).

The prevalence of FSD was higher in menopausal women as compared with non menopausal women (Heidari M et al., 2019). Advanced age and longer duration of diabetes have been associated with an increased risk of ED in diabetic patients (Maiorino MI et al., 2014). Older adults are at higher risk to develop diabetes mellitus (Kirkman et al., 2012). Age is a non modifiable risk factor for diabetes. Age more than 60 years was an independent risk factor for diabetes-related complications despite good control of cardiovascular risk factors (Chew BH et al 2013). Thus, with double risk, SD is expected among older adults.

### **1.5.2 Systemic Hypertension**

Hypertensive is expected to rise by 60% by 2025, reaching 1.5 billion patients worldwide (Kearney PM et al., 2005). In ED and FSD, systemic arterial hypertension causes negative impact on sexual response cycle. High blood pressure causes vascular changes in genitalia. Reduction of blood flow, smooth muscle hypertrophy and sclerosis of the cavernous arteries may interfere with the relaxation response and dilation occurring when there is sexual stimulation (Viigimaa M et al., 2011).

Different classes of antihypertensive drugs are commonly implicated in the development of SD in hypertensive patients. Available data clearly indicate that SD is more frequently seen in hypertensive patients than in normotensive individuals and higher prevalence of ED in treated than in untreated hypertensive patients (Viigimaa M et al., 2011), implying that hypertension treatment contributes to sexual dysfunction. Older group of anti-hypertensive, beta blockers and diuretics exhibit significantly worse sexual function than patients administered newer drugs, such as angiotensin receptor blockers, ACE-inhibitors, and calcium antagonists (Parthasarathy HK et al., 2011, Boydak B et al., 2005, Doumas M et al., 2006).

The implication of some antihypertensive drugs in causing ED is disputed by some researchers. They concluded that there is only minimal increase in the incidence of SD in patients on beta blocker therapy and the it was related to patient previous knowledge on the drug and its actions on sexual function (nocebo effect) (Silvestri A et al.,2003, Ko DT,et al., 2002). A large review of 35 000 patients with a variety of cardiovascular conditions treated with b-blockers showed a very small incidence of ED (5/1000) patients (Ko DT et al, 2002).

### **1.5.3 Hyperlipidemia**

Pathophysiology of hyperlipidemia and ED is vascular-related and suggested to be same in both ED and FSD. This association has been attributed to the impairment of blood flow through endothelium-dependent relaxation in smooth muscle cells of corpus cavernosum (Roumeguère et al., 2003) and impairment of vasocongestive and neuromuscular events that include increased clitoral length and diameter, as well as increased vaginal lubrication, wall engorgement, and luminal diameter (Gragasin FS et al., 2004)



There is a close relationship between hyperlipidemia and SD (Roumeguère et al., 2003, Esposito et al., 2009). The prevalence of hyperlipidemia (Total cholesterol >5.17 mol/l) is higher in ED compared to non-ED groups (70.6% vs. 52% in ED and non-ED groups respectively) ( $p=0.06$ ). High levels of total cholesterol and low levels of high density lipoprotein (HDL) cholesterol are important risk factors for ED (Vrentzos et al., 2007). There was a 1.32-fold (95% CI 1.04, 1.68) increase in the risk of ED for every 1.0mmol/l raised in total cholesterol.

Women with hyperlipidemia have significantly lower FSFI-domain scores as compared with age matched women without hyperlipidemia was first demonstrated by Esposito et al in 2009. FSFI score was found negatively correlated with age, body mass index, and triglyceride levels, and positively correlated with HDL cholesterol levels. The prevalence of FSD was higher in metabolic syndrome women than healthy post menopausal women (Martelli, V et al., 2015).

#### **1.5.4 Hormonal changes**

Sexual function is hormonal driven and it is complex as involving much different type of hormones (testosterone, oestradiol and certain peptides including oxytocin,  $\beta$ -endorphin and prolactin). Hormonal function may derail in older adults (Dennerstein et al., 2003).

Androgens enhance libido and the frequency of sexual acts but a causal relationship between changes in androgen levels and ED has not been proved (Carani C et al., 1990). Similarly, there was no significant correlation of total testosterone with erectile condition in aging men (Ernani et al., 2002). On the other hand, estrogen plays a significant role in regulating FSD. Level of estrogen has been shown to correlate with desire, sexual activity, sexual feelings and sexual problems in postmenopausal women

(Modelska K et al., 2003). Postmenopausal women experience SD twice more common as compared with pre-menopausal women (Gracia CR et al., 2007). There is a dramatic 5- to 10- folds reduction in levels of circulating estradiol during menopause (Hall J.E, 2015). Androgen level decreases with age, but appear not correlate with sexual function in women (Davison et al., 2005)

### **1.5.5 Beta blocker**

Beta blockers are a drug class that commonly use for systemic arterial hypertension and cardiovascular problem. It has wide heterogeneity in terms of selectivity to adrenergic receptors, intrinsic sympathetic activity, and vasoactive effects. Vasoconstriction is one of the reasons that contribute to vasculogenic SD through reduced blood supply.

Sexual dysfunctions arise from their action on diminishing beta 2-vasodilation and creating unopposed alpha 1-vasoconstriction that alters normal cavernosal dynamics (Rosen RC et al., 1988). In addition, non selective beta blockers especially have been found to reduce the serum testosterone and thus, sexual drive. However, there is only minimal increase in the incidence of sexual dysfunction in patients on both topical and systemic beta blockers therapy. The increment may be related to nocebo effect, which is due to patient knowledge and expectation of the side effect rather than organic cause (Silvestri A et al., 2003; Ko DT et al., 2002).

There are many types of topical glaucoma agents available in treating POAG. Numerous studies were one to examine the association between glaucoma therapy and ED. Geoffrey law et al demonstrated that topical beta blocker use in open angle glaucoma patients did not show a significant association with a diagnosis of ED. Greater number of glaucoma eyedrops was also not significantly associated with a diagnosis of ED. Individual class of glaucoma medications, including beta blockers,

prostaglandin analogues, carbonic anhydrase inhibitors and alpha-agonists were not associated with a diagnosis of ED. Total number of topical glaucoma medications does not affect the severity of ED based on ED score.

## **1.6 Rationale of Study**

Happy aging is currently the main debate in gerontology. Aging affects both SD and glaucoma. Visual stimulation is an important factor for sexual desire and arousal (Heather et al., 2008). Constricted visual field in glaucoma may affect sexual desire and arousal, which indirectly play a role in SD. There is no doubt that SD and glaucoma affect QoL especially in psychosocial issues, adherence and persistence to medications. Early detection of SD among patients with POAG may help improve their QoL. The main aim of treatment in POAG is to preserve vision and to ensure a good QoL. Identification and treatment of SD may also help improve QoL. Good QoL leads to better adherence and persistence to treatment which is also contributing to retardation of glaucomatous damage. There is limited study on sexual dysfunction in POAG patients. To the best of our knowledge there is no such study that has been conducted in Malaysia or Asia.

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