EVALUATION OF STRESS AND SLEEP QUALITY AMONG JUVENILE OPEN ANGLE GLAUCOMA PATIENTS USING MALAY TRANSLATED PERCEIVED STRESS SCALE (M-PSS) AND PITTSBURGH SLEEP QUALITY INDEX (M-PSQI)

BY

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DISCLAIMER

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

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LIST OF ABBREVIATIONS

BCVA	Best corrected visual acuity
CI	Confidence interval
DSM- IV	Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)
JOAG	Juvenile open angle glaucoma
LogMAR	Logarithm of the Minimum Angle of Resolution
IOP	Intraocular pressure
HPA	Hodapp- Parish-Anderson
HPA	Hypothalamic-pituitary –axis
HVF	Humphrey Visual Field
MD	Mean Deviation
OSA	Obstructive sleep apnoea
SAS	Sleep apnoea syndrome
SAM	Sympathetic adreno-medullary
ipRGC	intrinsically photosensitive retinal ganglion cells
POAG	Primary open angle glaucoma
PACG	Primary angle closure glaucoma
PSQI	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SE	Standard error
SLT	Selective laser trabeculoplasty

VCDR	Vertical cup disc ratio
HRPB	Hospital Raja Permaisuri Bainun
HRPZ	Hospital Raja Perempuan Zainab
HTAA	Hospital Tengku Ampuan Afzan
HUSM	Hospital Universiti Sains Malaysia

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Abstrak

Pengenalan

Glaukoma adalah penyakit kronik yang mengakibatkan kemerosotan neuropatik saraf optik yang progresif dan berakhir dengan kebutaan kekal. Glaukoma sudut terbuka juvana (JOAG) adalah subset kumpulan glaukoma sudut terbuka primer (POAG) dan dikaitkan dengan pewarisan dominasi autosomal. Ia biasanya dikesan seawal umur 3 hingga 40 tahun. Medan penglihatan terhad yang dihadapi oleh pesakit diusia ini akan menghalang kemampuan bekerja serta menganggu kesihatan fizikal dan mental. Kajian terhadap stres dan kualiti tidur dalam kalangan pesakit JOAG adalah sangat terhad berbanding pesakit kronik lain.

Objektif

Kajian ini bertujuan untuk menilai tahap anggapan stres dan kualiti tidur dalam kalangan pesakit JOAG di Malaysia berbanding kumpulan kawalan serta mengenalpasti faktor berkaitan dengannya.

Kaedah Kajian

Kajian perbandingan keratan rentas melibatkan 128 subjek (64 JOAG dan 64 kumpulan kawalan) dijalankan di antara bulan Julai 2020 hingga Jun 2021 di 4 pusat tertiari mata di Malaysia. Borang kaji selidik Perceived Stress Scale (PSS) dan Pittsburgh Sleep Quality (PSQI) versi Bahasa Malaysia telah digunakan. Data sosiodemografi dicatatkan. Kumpulan JOAG diperiksa secara terperinci berdasarkan keputusan pemeriksaan klinikal. Analisa regresi linear digunakan untuk mengenalpasti faktor-faktor berkaitan dengan anggapan stres dan kualiti tidur pesakit JOAG.

Keputusan

Usia min untuk peserta kajiselidik ialah 31.44±6.38 tahun dan mempunyai kadar perbandingan jantina yang sama. Skor min untuk soal selidik M-PSS pesakit JOAG ialah 13.70±3.87 dan 8.72±3.96 untuk kumpulan kawalan. Skor min untuk soal selidik PSQI pesakit JOAG dan kawalan ialah 7.33±2.30 dan 4.67±2.12 masing-masing. Pesakit JOAG memaparkan anggapan stres dan masalah tidur yang ketara berbanding kumpulan kawalan ($p<0.01$). Analisis univariasi dan multivariasi linear regresi mendapati status pekerjaan dan tahap keterukan glaukoma dikaitkan dengan skor M-PSS dan M-PSQI. Pengangguran dalam kalangan JOAG menunjukkan skor M-PSS yang 2.59 kali lebih tinggi berbanding pesakit yang bekerja sendiri (95% CI 0.12- 5.06; $p = 0.040$). Tahap glaukoma yang teruk menunjukkan 3.76 markah M-PSS yang lebih tinggi berbanding glaukoma tahap ringan (95% CI 0.65-6.86; $p = 0.019$). Pesakit JOAG yang tidak bekerja juga menunjukkan skor M-PSQI yang 1.68 kali lebih tinggi daripada subjek yang bekerja sendiri (95% CI 0.22- 3.14; $p = 0.025$). Di samping itu, tahap glaukoma yang teruk memaparkan skor M-PSQI yang 2.28 kali lebih tinggi berbanding glaukoma tahap ringan (95% CI 0.45-4.11; $p = 0.016$). Terdapat perkaitan sederhana positif antara skor M-PSS dan M-PSQI ($P<0.05$).

Kesimpulan

Skor min untuk M-PSS dan M-PSQI adalah lebih tinggi dalam kalangan pesakit JOAG. Pengangguran dan keterukan glaukoma dikaitkan dengan tekanan dan gangguan tidur dalam kalangan pesakit JOAG. Kerjasama di antara pakar oftalmologi dan pakar psikiatri adalah penting dalam rawatan pesakit JOAG secara holistik.

Abstract

Introduction

Glaucoma is a chronic disease that causes progressive optic neuropathy resulting in irreversible blindness. Juvenile open angle glaucoma (JOAG) is a rare variant of primary open angle glaucoma that is associated with autosomal dominant inheritance, primarily affecting those aged between 3 to 40 years old. As JOAG patients are young and actively contributing towards financial stability of the country, this disease may render them blind and incompetent if they are not managed holistically. Stress and sleep quality were studied among other patients with chronic disease. However there were few literatures about stress and sleep quality among JOAG.

Purpose

The aim of the study was to evaluate stress and sleep quality among JOAG patients compared to control group. Also, the study aimed to determine the factors associated with stress and sleep quality among JOAG patients in Malaysia

Materials and Method

A comparison cross sectional study involving 128 participants (64 JOAG patients and 64 control group) was conducted between July 2020 and June 2021 in 4 tertiary centres in Malaysia. The Malay version of Perceived Stress Scale (M-PSS) and Pittsburgh Sleep Quality Index (M-PSQI) questionnaires were administered. Sociodemographic data was documented. The JOAG group was evaluated on their clinical findings as well as latest treatment regime. Linear regression analysis was used to identify the associated factors for stress and sleep quality among JOAG group.

Results

The mean age of the participants was 31.44±6.38 years with no sexual predilection. The mean M-PSS score among the JOAG group was 13.70±3.87 and 8.72±3.96 in the control group respectively. The mean score for M-PSQI was 7.33± 2.30 in the JOAG group and 4.67± 2.12 in the control group respectively. Significant higher perceived stress and sleep quality scores ($p<0.05$) were observed among JOAG group. From the univariate and multivariate linear regression analysis, occupational status and glaucoma severity on the worse eye showed significant interaction with the M-PSS and M-PSQI scores. Unemployed subjects had 2.59 higher M-PSS score than self employed (95% CI 0.12- 5.06; $p = 0.040$) and severe glaucoma showed 3.76 higher M-PSS score than those with mild glaucoma (95% CI 0.65-6.86; $p = 0.019$). For M-PSQI score, unemployed subjects revealed 1.68 higher score than self employed subjects (95% CI 0.22- 3.14; $p = 0.025$), while severe glaucoma patients showed 2.28 higher score than those with mild glaucoma (95% CI 0.45-4.11; $p = 0.016$).There was positive moderate association between M-PSS and M-PSQI scores ($P<0.05$).

Conclusion:

The mean score for M-PSS and M-PSQI were significantly higher among JOAG patients. Unemployment and severity of glaucoma were associated with stress and sleep disturbances among JOAG patients. Collaboration between ophthalmologists and psychiatrists is vital in the management of JOAG patients holistically.

CHAPTER 1

INTRODUCTION

1.0 INTRODUCTION

Glaucoma is defined as a chronic disease with progressive optic neuropathy, characterised by morphological changes of the optic nerve head (ONH) and retinal nerve fibre layer (RFNL) with corresponding visual field (VF) defect (Foster *et al*., 2002). It is described as silent visual thief, as most of the patients are usually asymptomatic and only seek attention during the terminal stage of disease. Glaucoma in general is classified as primary and secondary glaucoma. There is no identifiable cause for primary glaucoma, while secondary glaucoma is attributed to trauma, lens related, neovascularisation and uveitis (Foster *et al*., 2002).Primary glaucoma can be classified into open and closed angle based on its morphological angle configuration (Bagnasco *et al*., 2020). Primary open angle disease can be further divided into primary open angle glaucoma (POAG), POAG suspect and ocular hypertension. Juvenile open angle glaucoma is a subset of open angle glaucoma that affects those aged more than 3 years and less than 40 years old (Ciociola and Klifto, 2022).

1.1 Prevalence of glaucoma

The World Health Organization (WHO) reported that around 2.2 billion people are suffering from impaired vision or blindness globally, with only half of them who sought treatment (WHO, 2019). Data reported that of the 2.2 billion people, the visual impairment or blindness in about 1 billion people could have been prevented or has yet to be addressed (WHO, 2019). The causes for visual impairment, are unaddressed refractive error, which is the major cause for visual impairment (123.7 million),

followed by cataract (65.2 million), glaucoma (6.9 million), corneal opacity (4.2 million) and diabetic retinopathy (3 million) (WHO, 2019). Based on the global estimates on visual impairment by WHO, it is reported that at least 76 million people are suffering from glaucoma worldwide, the leading cause of irreversible blindness (WHO, 2019). Tham *et al* (2014) reported that the global prevalence of glaucoma was 3.54% (Tham *et al*., 2014). It is estimated that by 2040 the prevalence of glaucoma patients will increase up to 111.8 million among those aged between 40-80 years old (Tham *et al*., 2014). It is more alarming to note that the prevalence of glaucoma in Africa and Asia will rise significantly in the upcoming years with possible increment of 18.8 million POAG patients and 9.0 million PACG patients respectively (Tham *et al*., 2014). Based on a meta-analysis in 2013, Asia contributed to 60% of glaucoma patients, with Africa in the second place (13%) (Tham *et al*., 2014). Review on the prevalence of glaucoma in Asia reported that East (China, Japan, South Korea, Mongolia) and South Central Asia (India,Iran, Nepal, Sri Lanka were the highest, with higher prevalence of PACG in China , while Japan and South Korea recorded more POAG rates (Chan et al., 2016).

As for the prevalence of glaucoma in South East Asia, the occurrence is lower than the African decent but higher than the Caucasion population (Tham e*t al*., 2014). The subtypes and risk of glaucoma vary according races and countries (Chan *et al*., 2016; Tham *et al*., 2014). Study also stated that glaucoma is more prevalent among male patients (Tham e*t al*., 2014). The Malaysia National Eye Survey II reported that among the causes of blindness in Malaysia, cataract (58.6%) is the commonest cause followed by diabetic retinopathy (10.4%) and glaucoma (6.6%) (Chew *et al*., 2018). This survey was conducted among Malaysian residents aged more than 50 years old,

hence the percentage of glaucoma depicted the prevalence among those aged more than 50 years old. Congenital glaucoma and JOAG would not have been included in the survey.

1.2 Juvenile Open Angle Glaucoma (JOAG)

JOAG is a rare variant of open angle glaucoma that is linked to be autosomal dominant inheritance (Kwun *et al*., 2016; Turalba and Chen, 2008). It occurs between the age of 3 to 40 (Ciociola and Klifto, 2022). The prevalence of JOAG in the United States was reported to occur in 1 in 50000 individuals (Turalba and Chen, 2008). Fung *et al*., (2013) reported that JOAG constitutes 4% of the cases of childhood glaucoma (Fung *et al*., 2013). To our best knowledge, there were no studies that had highlighted the prevalence of JOAG among Malaysians although it was described among different ethnic origins like Irish, Italian, Spanish, American, African-American, English Chinese, Filipino and Japanese (Turalba and Chen, 2008)

Through the Mendelian inheritance pattern of autosomal dominant pattern, it was postulated that *myocilin (MYOC)* gene mutation is associated with JOAG occurrence (Mimivati *et al.,* 2014; Turalba and Chen, 2008). In a large Malay pedigree population study on myocilin (*MYOC)* gene, it was reported that this gene was detected in 32 members out of 122 family members, of which, 21 were already treated for JOAG (Mimivati *et al.*, 2014). The study also reported incomplete penetrance observed among the members with *MYOC* gene mutation that is located at chromosome 1q23-q25(Richards *et al.*, 1994). In addition, there are more than 80 mutations reported in *MYOC* gene globally, of which, Arg46Stop was considered as the disease-causing-mutation among Asians (Hewitt *et al*., 2008). Another study reported that the *MYOC*

gene mutation was detected in up to 36% among JOAG patients while only 2-4% was detected among POAG patients (Turalba and Chen, 2008). The exact pathogenesis of increased IOP leading to glaucoma among those with *MYOC* gene mutation is yet to be elucidated, although few theories have been linked to it (Turalba and Chen, 2008). Among the postulated theories were overproduction of the myocilin protein in the trabecular meshwork caused abnormal accumulation and impediment of the aqueous outflow,increased outflow resistance in the trabecular meshwork and impaired function of the normal myocilin protein (Turalba and Chen, 2008). The resultant effect is increase in IOP that causes optic neuropathy. Other than *MYOC* gene, *CYP1B1* mutation is also linked to JOAG occurrence (Su *et al.*, 2012; Turalba and Chen, 2008). This gene belongs to the CYP450 superfamily on chromosome 2p21.Its mutation was associated with anterior segment defect (Su *et al.*, 2012). Turalba and Chen (2008) cited that mutation of both CYP1B1 and MYOC gene was associated with earlier onset of glaucoma (mean age of 27) (Turalba and Chen, 2008). However , CYP1B1 mutation can also occur independently in the absence of *MYOC* gene mutation and may still predispose towards development of JOAG (Su *et al.*, 2012; Turalba and Chen, 2008). Besides *MYOC* and *CYP1B1*genes, other genes which are associated with JOAG occurrence include optineurin *(OPTN*), neurotrophin 4 (*NTF4)* and WD repeat domain 36 (*WDR36*) (Willoughby *et al.*, 2004). Hence, genetic screening of probands associated with JOAG in our community should be considered for presymptomatic diagnosis and early treatment to prevent irreversible vision loss.

Unlike primary congenital glaucoma that occurs at very early age with significant ocular changes like epiphora, photophobia,buphthalmos,corneal clouding, Haab striae, anterior segment dysgenesis and optic disc cupping, JOAG patients are

relatively asymptomatic and usually present at advance stage of glaucoma with high intraocular pressure and severely depressed visual field (Aponte, 2010). Gupta *et al*.,(2018) cited in their study that about 15% of JOAG patients were blind bilaterally upon presentation (Gupta, Ganesan, *et al.*, 2018). Another study showed that 1/3 of JOAG patients were diagnosed by chance during a follow up to the ophthalmologist without a definite symptom (Kwun *et al.*, 2016). Also, it is reported that JOAG has male preponderance with myopia and prominent iris processes (Kwun *et al.*, 2016; Turalba and Chen, 2008)

There are various treatment modalities for glaucoma in young adults that are similar to POAG management. This includes medical therapy with IOP lowering agents, laser trabeculoplasty, surgical interventions such as trabeculectomy, goniotomy, and glaucoma drainage device (GDD) (Gupta, Ganesan, *et al.*, 2018). In contrast to POAG, the treatment for JOAG patients is challenging owing to its rapid progression and often refractory to medical treatment (Turalba and Chen, 2008). Besides, lack of compliance among young adults in medical therapy also hinders IOP optimization among them. A study in India demonstrated the efficacy of selective laser trabeculoplasty (SLT) among JOAG patients (Gupta, Ghosh, *et al.*, 2018). It was reported that almost all JOAG patients had 20 % reduction in IOP by 12 months (Gupta, Ghosh, *et al.*, 2018). Goniotomy is usually performed in those with childhood glaucoma, however, a study reported that JOAG patients also showed significant improvement following minimally invasive glaucoma surgery (76.5%) (Yeung and Walton, 2010).

Trabeculectomy has been the primary operation for JOAG. Pathania *et al.*, (2014) reported that the success rate for trabeculectomy without MMC was 89% at first 3 years with younger age being a significant risk factor for bleb failure (Pathania *et al.*, 2014).

Another study in Taiwan reported that there was no significant difference in the success rate following augmented trabeculectomy in JOAG patients (Tsai *et al.,* 2003). In fact, there were more post op complications such as hypotony maculopathy and bleb related infection (Tsai *et al.*, 2003). Hence, the usage of antimetabolites should be meticulous in this group of patients. As for GDD, Ciociola et reported favorable outcome in the management of IOP among JOAG patients (Ciociola and Klifto, 2022).

Many studies have reported on the importance early screening for glaucoma among the probands of known glaucoma patients especially first degree relatives (Chelvaraj *et al.,* 2022; Rajendrababu *et al.,* 2014). Hence it is pivotal to screen the young population especially those with significant family history of glaucoma for pre-symptomatic or early detection to halt the progression of the disease and preserve vision. As JOAG patients have longer life expectancy, impaired vision at early age would impede their productivity and exert significant medical and economic burden to developing countries like Malaysia. Wittenborn *et al.,*(2013) reported that the estimated expenditure due to eye disorders among adults aged less than 40 in 2012 was USD27.5 billion per year (Wittenborn *et al.,* 2013). Keeping in concern with quality adjusted life years (QALY), it was reported the cost of quality-of-life losses amplified the entire burden by USD10.8 billion, with total cost of eye disease and vision loss to USD38.2 billion for population younger than 40 years (Wittenborn *et al.,* 2013). Also, the rate economic burden may be even higher than recorded due to underestimation of number of patients with impaired vision (Wittenborn *et al.,* 2013).

1.3 Stress

Stress is the physiological reaction and adaptation of the body to any demand for transform (Sheldon *et al*., 2007; Yf and Yt, 2018). Cohen *et al.,* (1995) coined stress as "a process in which environmental demands tax or exceeds the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease"(Cohen *et al.,*1995). The pathogenesis of disease is influenced by stressful events that result in negative affective states like anxiety and depression which in turn affect the biological process of the disease (Sheldon *et al.,* 2007). Stress is broadly classified into eustress and distress (Kupriyanov *et al.,* 2014). Eustress is termed as positive stress with health and behavioural benefits (Kupriyanov *et al.,* 2014). Distress is a negative stress that occurs when the burden exceed the ability of the person to cope (RS., 1993; Sheldon *et al*., 2007).

The American Psychological Association and Australian Psychological Society in 2015 classified stress into three categories, which are acute, episodic acute and chronic stress (APA, 2008). Acute stress is the effect of demands and pressure of recent and nearest future and often does not cause extensive damage (APA, 2008). The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) stated acute stress disorder (ASD) as a trauma and stressor-related disorder regarded by negative mood, intrusive memories, dissociation, avoidance, and/or hyperarousal experienced in the first month after a traumatic event (Appendix) (Bryant, 2017). Episodic stress is recurrent episodes of acute stress commonly encountered by type A personality while chronic stress is often associated with functional and behavioural changes (Koval, 2016). PTSD occurs in the event of stressful incidents such as accidents, natural disasters, sudden death or war (Koval, 2016).

Research elucidated that symptoms of extreme stress have common characteristics of anxiety and depression. The physiology of stress can be explained by the basis of association between sympathetic adreno-medullary (SAM) system and hypothalamic-pituitary-adrenocortical (HPA) axis (Khan, 2016; Sheldon *et al.,* 2007). SAM activation by the cerebral cortex that perceives a situation as a stressor causes transmission of stimulus via the hypothalamus that initiates the fight or flight response (Khan, 2016). This circuit also activates the adrenal medulla to secrete catecholamines that result in increased blood pressure and heart rate, sweating and vasoconstriction (Khan, 2016). HPA activation in turn secretes corticotrophin releasing hormone (CRH) that stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH activates the release glucocorticoids like cortisol by stimulation of the adrenal cortex. Cortisol affects carbohydrate metabolism and controls inflammation. Continuous activation of HPA in certain conditions like chronic stress is associated with serious diseases (Khan, 2016). The effect of activation of neurotransmitter cascades by stress eventually leads to mood disorders like anxiety and depression (Ardayfio and Kim, 2006; Van Praag, 2004). Combination of emotional arousal and neuroendocrine stimulation were linked towards development of chronic insomnia (Khan, 2016). An epidemiological study reported that chronic insomnia was also linked with behavioural disorders like anxiety and depression (Shaver *et al.,* 2002).

1.4 Perceived Stress Scale

As JOAG patients are young adults who are still financially productive, impaired vision due to disease progression may exert as a stressor. A comparative study reported that there was increased incidence for the visually impaired young adolescents to succumb

into depression due to impaired coping skills to manage stress (Hallemani *et al.*, 2014). Often, management of glaucoma in the hospital setting only focuses on the target IOP control and objective visual field changes. However, least attention is given towards their psychosocial wellbeing. Hence, we are unable to provide a holistic management on this group. So, a psychometrical valid measure of perceived stress would enable us to determine and manage stressed patients as a whole.

Perceived Stress Scale (PSS) is the commonly used psychometric instrument to determine the perception of stress *(Cohen et al.,* 1983). Perceived stress is termed as the emotions felt by an individual about the amount of stress faced by them at given situation or time. It compounds the feelings of an individual of not being able to control or predict some events in their life and its effect on their confidence level (Cohen *et al.,* 1983). Each individual may appraise differently to a similar negative event in their life, owing to factors like personality, support and coping resources that influence their reaction (Cohen *et al.,* 1983; Sheldon *et al.,* 2007). Hence perceived stress reflects the relation between individuals and the situation they appraise as stressful (Cohen *et al.,* 1983). This scale enables us to understand how different situations affect our feelings and our perceived stress. The scale contains 10 items and uses a 5-point Likert scale: 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often. The total scores are obtained by summing up all the items, with items number 4, 5, 7, and 8 are reversed-scored. The maximum score is 40, with scores ranging less than 13 is regarded as low stress. Score ranging between 14 to 26 is moderate stress and score higher than 27 is higher perceived stress (Scale *et al.,* 1983). Higher scores reflect higher and longer duration of stress (Cohen *et al*., 1983). The reliability of PSS was 0.85 (Ayaki *et al.,* 2016).

1.5 Sleep

Sleep is a biological process that is vital for life and overall wellbeing. It functions to maintain optimal brain function and systemic physiology such as body metabolism, appetite regulation, and internal homeostasis (Wang *et al*., 2013). Normal healthy sleep is characterized by adequate duration, good quality, appropriate timing and regularity, and the absence of sleep disturbances and disorders (Wang *et al.,* 2013). Sleep quality is generally assessed as total sleep duration, sleep onset latency, sleep efficiency, wakefulness after sleep onset, and daytime sleepiness (Mollayeva *et al.,* 2016). Good sleep quality is indicated by shorter sleep latencies, sufficient total sleep time, reduced wake after sleep onset, and alertness during daytime (Mollayeva *et al.,* 2016). Sleep has been historically be divided into rapid eye movement (REM) sleep and of non-rapid eye movement (NREM) (Wang *et al.,* 2013).

REM and NREM sleep are associated with various physiologic changes such as brain activity, heart rate, blood pressure, sympathetic nervous system activity, and muscle tone, blood flow to the brain, respiration, airway resistance, renal function, endocrine function, body temperature, and sexual arousal (Wang *et al.,* 2013). It was reported that nearly 70 million people in the US and about 45 million people in Europe are suffering from chronic sleep disorder that impacts daily functioning and health (Wang *et al.,* 2013). Insufficient sleep may lead to alterations in the neuroendocrine stress response system, ultimately causing stress-related disorders such as mood disorders and depression (Wang e*t al.,* 2013).

The International Classification of Sleep Disorders (ICSD-2) classified sleep disorders into seven categories which are insomnia disorders, sleep related breathing disorders, sleep related movement disorders, central disorders of hypersomnolence, parasomnia,

circadian rhythm sleep disorders and other sleep disorders (Sateia, 2014). Mollayeva *et al.,* (2016) reported that sleep disorders and other factors such as psychological distress, pain, lifestyle factors, environmental factors and medications were associated with sleep dysfunction (Mollayeva *et al.,* 2016).

On the other hand, sleep disorders such as obstructive sleep apnoea (OSA) was found to be a risk factor for glaucoma (Lee *et al.,* 2016; Mojon *et al.,* 2000). Study reported that sleep apnoea syndrome (SAS) was more prevalent among POAG patients in their study (Mojon *et al.,* 2000). Lee *et al.,* (2016) explained that sleep disturbance among obese Korean people correlated with the prevalence of glaucoma in this group (Lee *et al*., 2016). The study reported that overweight individuals, who slept less than 7 hours and more than 9 hours were found to have higher risk of glaucoma (Lee *et al.,* 2016).

SAS is characterised by cyclical upper airway obstruction during sleep resulting in hypoxia and optic nerve hypoperfusion (Mojon *et al.,* 2000). Following episode of hypoxia and hypercapnia, the patient is aroused from sleep with resultant sympathetic activation (Mojon *et al.,* 2000). Repetitive sympathetic activation leads to cardiovascular diseases and systemic hypertension (Mojon *et al.,* 2000). Generally, obese patients with history of snoring are vulnerable to SAS (Mojon *et al.,* 2000). The resultant effect is sleep disturbance denoted as daytime sleepiness and difficulty in initiating sleep (Jean-Louis *et al.,* 2008)

Literature review stated that sleep deprivation is postulated to cause short and long term health effects (Vgontzas *et al.,* 1998). Interrupted sleep is found to cause increased sympathetic activation that results in transient hemodynamic, vasoconstrictive and prothrombotic cascades with a stress response (Vgontzas *et al.,* 1998).. The resultant effect is on the cardiovascular system and mental status (Vgontzas *et al.,* 1998). It is

noteworthy that long term effect of sleep disruption in may result in higher incidences on non communicable diseases such as metabolic syndrome, hypertension and dyslipidemia (Vgontzas *et al.*, 1998).

As for glaucoma patients, study showed that depletion of of intrinsically photosensitive retinal ganglion cells (ipRGC) due to of oxidative stress in glaucoma is found to alter the photic transduction to the circadian rhythm that is pivotal for sleep cycle .(Huber, 2011). Also, melatonin is the most important neurotransmitter that modulates the circadian rhythm via the suprachiasmatic nucleus (SCN) (Huber, 2011). Research revealed that melatonin also has neuroprotective property and an active antioxidant in the retina (Detoxification and Avoidance, 2005). Its production is stimulated by photic input of certain wavelegth (460-480nm) via the retinal hypothalamic tract to SCN (Detoxification and Avoidance, 2005). Loss of ipRGC results in impaired photic input and hence reduced melatonin production. This vicious cycle in turn leads to further reduction of ipRGC, disturbed circadian cycle and depression via the hypothalomo-pituitary axis (HPA) interaction (Drouyer *et al.*, 2008). Besides, melatonin is also involved in the homestasis of energy flow via activation of brown adipose tissue (Cipolla-Neto *et al.*, 2014). Hence reduced melatonin production causes incresed insulin resistance, glucose intolerance and metabolic diseases (Cipolla-Neto *et al.*, 2014).

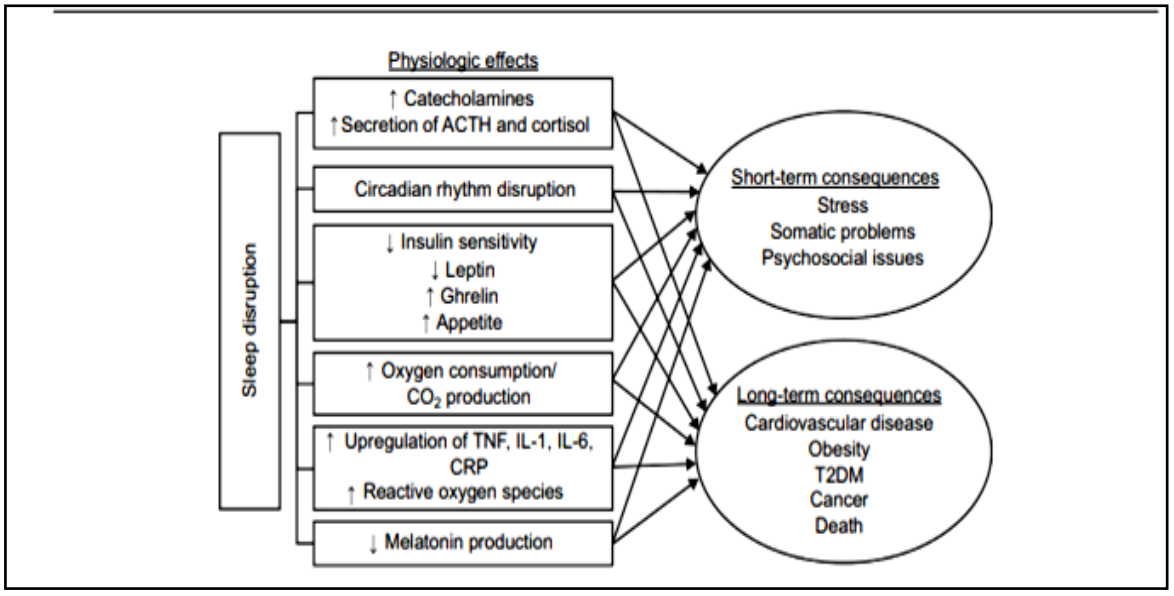

Figure 1: Proposed mechanism by which sleep disruption results in short and long term effects.Adapted from Medic et al., 2017

Notes: ↑, increase; ↓, decrease.

Abbreviations: ACTH, adrenocorticotropic hormone; CO2 , carbon dioxide; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; T2DM, type 2 diabetes mellitus

1.6 Pittsburgh Sleep Quality Index (PSQI)

As it is challenging to diagnose sleep dysfunction subjectively, the Pittsburgh Sleep Quality Index (PSQI) was developed in 1988 to provide a validated and standardized measure of sleep quality (Buysse *et al.*, 1989). The PSQI is a self-rated questionnaire that consists of 19-items that measures subjective sleep quality over the previous month. The 19 individual items in PSQI are grouped into seven components that assess various aspects of sleep which are sleep quality (1 item), sleep latency (2 items), sleep duration (1 item), sleep efficiency (3 items), and sleep disturbance (9 items), sleep medication (1 item) and daily dysfunction (2 items) (Buysse *et al.*, 1989). The score range in each

component is between 0 to 3 (Buysse *et al.,* 1989). The PSQI global score is obtained by calculating the total scores of the seven components, ranging from 0 to 21. The global PSQI score of more than 5 indicates poor sleepers, while total score of 5 and less indicate good sleepers (Buysse *et al.,* 1989). The internal consistency of the original PSQI score was 0.83 with diagnostic sensitivity and specificity of 89.6% and of 86.5% respectively (Buysse *et al.,* 1989). Due to its high internal consistency, the PSQI was translated to other languages such as Greek, Persian and Chinese language to suit the local community. The Malay version of questionnaire was developed by Farah *et al.,(*2019) and showed comparable results as other vernacular languages worldwide with acceptable internal consistency, (Cronbach's alpha of 0.74) (Farah *et al.,* 2019). The total score from the seven components determines the sleep quality. Ayaki *et al.,* (2016) cited that patients with advanced glaucoma in Japan suffer from sleep disorder , however the number of glaucoma patients suffering from sleep disorder in the study may have been underestimated (Ayaki *et al.,* 2016).

1.7 Sleep and stress in chronic diseases

The effects of stress on sleep disturbance have long been established(Almojali *et al.,* 2017; Da Estrela *et al*., 2021; Khan, 2016). Literature review also revealed that factors relating to stress and anxiety are the predisposers for disturbed sleep in general population (Buysse *et al.,* 1989) In a study among medical students in Saudi Arabia, higher level of stress is associated with disturbed sleep among the medical students (Almojali *et al.*, 2017). Also, the study revealed the intake of stimulants such as caffeinated beverages and energy drinks that affect sleep quality (Almojali *et al.*, 2017). In another study involving patients with chronic disease like diabetes mellitus, it was

reported that diabetic patients exhibited impaired sleep quality as compared to general population (Darraj *et al.*, 2018). Patients with chronic diseases often succumb to disease related distress due to the duration of the disease, lifelong treatment modality, medication adherence, and the need for regular follow up (Vancampfort *et al.*, 2017). These factors trigger a continuous cascade of stressor that eventually cause sleep deprivation among patients with chronic disease (Vancampfort *et al.*, 2017). Also previous studies reported higher rate of anxiety and depression among glaucoma patients, particularly POAG and PACG patients (Ayaki *et al.*, 2016; Berchuck *et al.*, 2020; Tharmathurai *et al.*, 2021). Study reported that factors such as disease chronicity, frequent hospital visits, multiple drugs and expenses concerning to treatment such as transportation and medications influence mental health of glaucoma patients (El-Mogy *et al.*, 2014). Also, fear of losing eyesight among glaucoma patients could be a source of stress (El-Mogy *et al.*, 2014). Hence, we postulate that glaucoma patients would have higher PSS score.

1.8 Rationale of the study

Adolescents are deemed to be at the peak of their career development and education. They have the capacity to create a positive psychosocial development at this stage. On the other hand, JOAG patients who are suffering from this potentially blinding disease may suffer from disease related distress, impaired sleep quality and limitation in activities of daily living. As JOAG patients have longer lifespan, the burden of leading life with glaucoma and its treatment drastically affect their quality of life. They are often bound with commitments to their family to provide financially. Also, career development would be another obstacle owing to the visual disability. They need to be motivated to cope with the disease while ensuring compliance to the treatment. The aim of the glaucoma treatment is to let these young adults to be independent and able to function as a normal person. The lifelong treatment and follow ups for glaucoma should not impede their psychosocial development nor burden them as a distress.

We aimed to address psychosocial disturbances among the JOAG patients gathered from different tertiary centres in Malaysia in our study. To our best knowledge, this is the first study that assesses sleep quality and stress among JOAG patients. Ophthalmology follow ups should also include psychiatric evaluation periodically apart from emphasizing on IOP control and medication adherence.

The outcome of this study will aid ophthalmologists to have better insight about the patients and customize the best management that suits the patient .The detection of sleep quality and perceived stress among JOAG would enable early referral to psychiatric team to improve treatment compliance and for social support. Also, this study would help us to improve our healthcare system as a whole in managing JOAG patients by detection of modifiable risk factors associated with stress and sleep quality.

1.9 References

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