

Sleep-disordered breathing a neglected risk factor in primary open-angle glaucoma

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Background: Sleep-disordered breathing (SDB) is accompanied by large swings in blood pressure and the repetitive hypoxic period during sleep, which may accelerate anoxic optic nerve damage seen in glaucoma. There are many associated risk factors in primary open-angle glaucoma (POAG), but recently, SDB, though a neglected one, is coming up as a risk factor. However, various studies have reported controversial findings. **Objective:** To evaluate the relationship between SDB and POAG. **Design:** A hospital-based case-control study. **Methods:** A total of 400 patients between 30–70 years were recruited from eye OPD between 2008–2010. They were divided into two groups, 200 cases with established POAG and 200 age and sex-matched healthy subjects with normal IOP in the control group. Detailed history, complete ophthalmic and ENT examination was made along with BMI, blood pressure and neck girth measurement. Both groups were interviewed with a questionnaire regarding SDB and were recorded on the Epworth sleepiness scale (ESS). **Results:** The mean age being 55.02 ± 8.66 in the POAG group and male predominance noted both in POAG and SDB patients with $ESS > 10$ was statistically significant ($p < 0.05$). Also, patients in the POAG group with $ESS > 10$ had more IOP and BMI, greater neck girth, high BP and more ENT problems with p -value $< 0,001$, which is highly significant, thus showing the relationship between SDB and POAG. **Conclusions:** Increased community awareness and earlier detection of glaucoma and its correlation with SDB results in decreased morbidity.

Keywords: Sleep, Breathing, Glaucoma, Disordered

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Introduction

Sleep-disordered breathing (SDB), or upper-airway obstruction during sleep or sleep apnoea initially demonstrated in the 1960s, is a common chronic disorder that results in recurrent nocturnal asphyxia, fragmented sleep, major fluctuations in blood pressure and increased sympathetic nervous system activity.[1] SDB represents a group of conditions having an abnormal respiratory pattern during sleep ranging from primary snoring to severe obstructive sleep apnoea.[2] Obstructive sleep apnoea (OSA) or obstructive sleep apnoea syndrome (OSAS) is a neglected and potentially disabling condition characterized by excessive daytime sleepiness [3], disruptive snoring, repeated episodes of partial or complete upper airway obstruction lasting 10 seconds to 60 seconds or more [4] due to hypotonia of the upper airway musculature during REM sleep [5] and nocturnal hypoxemia [6] which gets terminated by transient arousal that resumes ventilation. Sleep-disordered breathing affects up to 20% of the population between 30 and 60 years of age [7] and presents with daytime somnolence, tiredness, fatigue [8], the difficulty of concentration, headache, reduced work performance.

It is associated with several eye disorders that include floppy eyelid syndrome, optic neuropathy, non-arteritic anterior ischaemic optic neuropathy and papilloedema secondary to increased intracranial pressure, normal-tension glaucoma and primary open-angle glaucoma (POAG) [9-12]. POAG is defined as a chronic progressive optic neuropathy [13] in adults and is multifactorial. [14,15] It develops due to the death of retinal ganglion cells by elevated IOP and vascular insufficiency resulting from reduced ocular blood flow, decreased ocular perfusion pressure, generalized vascular deregulation or increased trans lamina cribrosa pressure [16]. and leads to typical visual field defects and increased cupping of the optic disc. [17]. OAG is the most common type of glaucoma and is estimated to be responsible for 50% of glaucoma cases [18]. The prevalence of glaucoma in the general population is between 1% and 2%. [19]. According to WHO, glaucoma is the second leading cause of blindness worldwide, and approximately 60 million people are diagnosed with glaucoma, and an estimated 8.4 million people are blind due to glaucoma.

Several risk factors are associated with SDB [20],

Like middle-aged males [7], black race, obesity, increased BMI, smoking, family history, large neck circumference, presence of upper airway abnormalities like enlarged tonsils and adenoids, nasal obstruction [21], diabetes, excessive alcohol consumption, hypothyroidism, acromegaly, hypertension, previous history of trauma or surgery of upper airways, abuse of chemicals like alcohol, sleeping pills, narcotics, barbiturates, sedatives and cigarettes. Few of these are also associated with POAG except high IOP, increasing age, optic nerve cupping and asymmetry, central corneal thickness less than 555 microns, high myopia and recently sleep-disordered breathing is being considered a probable risk factor for POAG.

Many studies have reported the association between glaucoma and OSAS, and most of them focused on the Prevalence of glaucoma in OSAS patients and indicated it as a risk factor. [9,22] McNab recently proposed an association between POAG and sleep apnea. [11] Hence, we conducted a study to investigate if there is any relationship between SDB and POAG.

Objective: To evaluate the relationship between sleep-disordered breathing and primary open-angle glaucoma.

Material and methods

Study design and setting: A random case-control study was conducted between 2008 and 2010 in a teaching medical institute in North India. A total of 400 patients between 30–70 years were recruited from eye OPD, dividing into two groups, 200 cases with established glaucoma in POAG group and 200 age and sex-matched healthy subjects with normal IOP in the control group.

Ethical consideration and permission: Ethical approval was taken from the institute's ethical committee and written informed consent from all subjects participating in the study.

Inclusion Criteria for POAG group

01. An intraocular pressure (IOP) \geq 21mmHg with or without
02. A cup to disc ratio (CDR) more than 0.5 or difference of CDR between two eyes $>$ 0.2 with thinning of the neuroretinal rim; the presence of any disc haemorrhages to strongly support the diagnosis
03. With glaucomatous visual field

- 04. Open Irido-corneal angle
 - 05. No history of ocular surgery or ocular
- Inclusion Criteria for Control group**
- 01. IOP <21mmHg.
 - 02. No evidence of glaucomatous optic
 - 03. Normal anterior chamber angle on slit lamp and gonioscopic
 - 04. Normal visual field test results
 - 05. No history of previous anti-glaucoma drugs, ocular surgery or ocular

Methodology

All subjects underwent complete ophthalmological examination, including best-corrected visual acuity using Snellen's chart, anterior chamber depth assessment using Van Herick technique, measurement of intraocular pressure (IOP) (Schiotz/ applanation tonometer), fundus assessment with an indirect ophthalmoscope and +78D lens for the presence of glaucomatous optic disc changes (cup-disk ratio > 0.5 or cup-disc asymmetry > 0.2, or partial or complete notching, and rim haemorrhages), Gonioscopy with Goldman three-mirror gonioscope and automated perimetry for visual field testing (30-2). ENT examination of nose and oropharynx for polyps, septal deviation, any mass in the nasal cavity, macroglossia, adenoids and enlarged tonsils was done. Measurement of blood pressure (BP) in mm Hg, basal metabolic index (BMI = weight in Kg divided by height square in meters) and neck circumference (NG) in centimetres was done for both POAG and Control groups.

For sleep-disordered breathing (SDB), all subjects were interviewed with a simple, self-administered questionnaire (Box 1) which is shown to provide a measurement of the subject's general level of daytime sleepiness[23] and were rated on the Epworth sleepiness scale (ESS)) devised at Epworth hospital in Melbourne, Australia and created by Murray Jones. The concept of the ESS was derived from observations about the nature and occurrence of daytime sleep and sleepiness. It is based on questions referring to eight such situations [23]. Subjects were asked to rate on a scale of 0-3 on the likelihood of being dozing off or falling asleep in the eight situations, depending upon the usual way of their life recently and distinguishing between dozing off and simply feeling tired. The numbers selected for the eight such situations [23].

Subjects were asked to rate on a scale of 0-3 on the likelihood of being dozing off or falling asleep in the eight situations, depending upon the usual way of their life recently and distinguishing between dozing off and simply feeling tired. The numbers selected for the eight situations in the ESS were added together to give a score for each subject, between 0 and situations in the ESS were added together to give a score for each subject, between 0 and 24. All the data thus obtained was arranged in tabulated form, and chi-square (χ^2) test analysis was performed for data comparison between POAG and control group patients. A probability value of less than 0.05 was considered significant.

Box1 The Epworth sleepiness scale

THE EPWORTH SLEEPINESS SCALE	
Name: _____	
Today's date: _____	Your age (years): _____
Your sex (male = M; female = F): _____	
How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:	
0 = would never doze	
1 = slight chance of dozing	
2 = moderate chance of dozing 3 = high chance of dozing	
SITUATION	CHANCE OF DOZING
Sitting and reading	
Watching television	
Sitting inactive in a public space (e.g. a theatre or a meeting)	
As a passenger in a car/bus for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	
My Total	
Thank you for your cooperation	

Results

We found that the mean age in the POAG group was 55.02 ± 8.66 years, and among the control group, it was 57.03 ± 9.28 years, and there was no statistically significant difference between the two groups. Table 1 shows the distribution of patients in two groups according to Epworth Sleepiness Scale for sleep-disordered breathing having 110 patients

(55%) in the POAG group with an ESS score of more than ten while 51 patients in the control group with ESS > 10. Statistically, this finding was highly significant (p < 0.001).

Table 1: Distribution according to Epworth Sleepiness Scale

ESS Score	POAG Group	%age	Control group	%age	Total
0-10	90	45	149	74.5	239
>10	110	55	51	25.5	161
Grand total	200	100	200	100	400

$\chi^2 = 36.19$; p < 0.001; **Highly Significant**

Table 2 shows the sex wise distribution in both study groups having more males (114) in the POAG group as compared to the control group, which had more females (108), and this was statistically significant (p < 0.05).

Table 2: Sex Distribution in POAG and Control Group

Sex	POAG Group	Control group	Total
Male	114	92	206
Female	86	108	194
Total	200	200	400

$\chi^2 = 4.85$; p < 0.05 ; significant

Table 3 shows male predominance (71 out of 110) in the POAG group with ESS score >10 (p-value < 0.05), while the control group had more females (30 out of 51) with an ESS score >10.

Table 3: Sex Distribution according to Epworth Sleepiness Scale

	POAG group with ESS > 10	Control group with ESS > 10
Male	71	21
Female	39	30
Total	110	55

Table 4 shows that in the POAG group, male patients had greater neck girth (103), higher BMI (87), more elevated BP (93) and more ENT manifestations (47) as compared to the control group and were statistically highly significant (p < 0.001).

Table 4: Gender-based distribution of Neck Circumference, BMI, High BP, Ent Problems And ESS

	POAG group		Control group	
	Males	Females	Males	Females
Neck Girth >42 cm	103	64	22	18
BMI >24	87	64	19	17
Presence of ENT problems	47	25	19	16

Blood Pressure >120/80 mm Hg	93	56	27	22
ESS > 10	71	39	21	30

Table 5 shows that 122 out of 200 patients with high intraocular pressure had an ESS score of more than 10.

Table 5: IOP and ESS score

IOP in mm Hg	ESS < 10	ESS > 10	Total
21-30	65	103	168
31-40	13	19	32
Total	78	122	200

Table 6 showed the distribution of 151 patients with ESS > 10 having greater neck circumference (93), higher BMI (90), more elevated BP (84) and more ENT manifestations (47) in the POAG group and were statistically highly significant (p < 0.001).

Table 6: Parameters in both groups

ESS >10	Neck Girth		BMI		Blood Pressure		ENT Problems	
	< 42 cms	>42 cms	< 24	> 24	<120/80 mm Hg	>120/80 mm Hg	Present	Absent
POAG group (110 patients)	17	93	20	90	26	84	47	63
Control Group (51 patients)	38	13	38	13	36	15	8	43
Chi square value	54.03		47.97		32.44		11.33	
P value	<0.001		<0.001		<0.001		<0.001	

Table 7: ENT problems in both groups.

ENT problems	POAG group	Control group
DNS	57	29
Nasal polyp	02	02
Mass in nasal cavity	01	Nil
Macroglossia	04	03
Adenoids	Nil	01
Enlarged Tonsils	08	Nil
Total	72	35

Discussion

We studied the relationship between Sleep-disordered breathing (SDB), a measure of obstructive sleep apnoea (OSA) and POAG, along with their relation to IOP, BMI, neck circumference and blood pressure. For SDB, excessive daytime sleepiness was assessed using the Epworth sleepiness scale (ESS), the concept of which was derived from observations about the nature and occurrence of daytime sleep and drowsiness [23]. In our study, we found the prevalence of SDB was higher in the POAG group [110 patients; 55% with ESS > 10 (Table 1)] than that in the control group

(26% with ESS score >10). The results were consistent with studies done by Onen et al. [19] They studied 212 outpatients with POAG and 212 outpatients without POAG and found a high prevalence of sleep-disordered breathing described by self-reported symptoms of snoring, excessive daytime sleepiness, and insomnia in the POAG group. Ohana et al [24] also reported high prevalence of OSAS in POAG patients and suggested that examination should include the history of the presence of snoring. Mojon et al [9] also found a higher prevalence of glaucoma (7.2%) in 69 patients with obstructive sleep apnoea compared to a 2% prevalence of glaucoma in a European population. They also found a positive correlation between the number of apneas experienced per hour and IOP, visual field loss variance, glaucomatous optic disc changes and the diagnosis of glaucoma, hence concluded that there might be a possibility that a dose-dependent relationship exists between OSA and the diagnosis and progression of glaucoma. Mojon also reported a 20% vs 11% prevalence of newly diagnosed sleep apnoea in POAG patients and hence found a significantly higher prevalence of OSA in the glaucoma patients compared with the control groups.[9] In a 5-year retrospective study, a statistically significant increase in the incidence of open-angle glaucoma in OSA patients compared with non-OSA patients was found. [25] Robert et al. [26] included 69 snorers in their study on eyelid hyperlaxity and obstructive sleep apnea syndrome and treated six patients (8.7%) for POAG, thus showing a significant incidental association between SDB and POAG. Another study on floppy eyelid syndrome and sleep apnea described that 1 of 8 patients having sleep apnea syndrome also had glaucoma.[27]. On the other hand, in a cross-sectional study published by Geyer et al [28] only 2% prevalence of glaucoma among 228 patients with sleep apnoea was found compared to the general Caucasian population and was not significant. Another study on 667 patients with newly diagnosed glaucoma from the diagnostic ICD9 database and a control group of 10 matched controls for each case of glaucoma found that there were seven cases (1.1%) of OSAS in 667 patients as compared with 32 (0.5%) in the control group which was not significant. [29].

Age is considered a risk factor for both POAG and OSA. The incidence of OSAS in the general population has also been reported to be the highest between 45 - 65 years of age. [30]

The mean age in our study was 55.02 ± 8.66 years in the POAG group with ESS >10, and 38.5% of patients were in the age group 41-50 years followed by 51-60 years and was very close to study by M Gyasi et al. [31] who found mean age of 53.2 years (median of 56) and a standard deviation of 16.3 with 23.6% below 40 years and Balbay et al [32] also found a mean age of 56 years in their study, but, S Y Wu et al [33] reported that prevalence of glaucoma increased with age in black participants, reaching 17% for those aged 70 years or older. In the general population, the prevalence of OSA is known to be 17% to 24% in men and 5% to 9% in women [7,30]. Some studies report male prevalence of POAG to be twice as high as females or vice versa, while others report no gender association at all. In our study, about 114 males were in the POAG group (Table 2), while the control group had more females. The results were similar to the study by Gyasi et al. [31], who found nearly twice as many males (n=292, 65.5% diagnosed with glaucoma compared to females (n=154, 34.5%). However, the study done by Al Monsouri F [34] found fewer males (41.6%) than females (58.4%). Also, we found male predominance (71 out of 110 patients) in the POAG group with ESS > 10 (Table 3) comparable to the study by Nahlah et al. [35] who also found more males in the OSA group than the control group ($p < 0.05$).

In contrast, Onen et al found more females than males in POAG and control groups [19]. Intraocular pressure is an important risk factor for glaucomatous optic neuropathy and obesity, measured as body mass index (BMI), may increase blood viscosity and episcleral venous pressure and damage aqueous outflow facility [36,37]. A few studies [38,39] suggested a relationship of IOP or ocular hypertension to BMI or obesity. We found 122 patients with increased IOP and 90 out of 110 patients with BMI > 24 in the POAG group with SDB (ESS > 10), and the incidence of BMI > 24 was higher in males (87). The studies in favour of our study are the Beaver Dam Eye Study that found a higher IOP association with higher BMI [38] and a study of Japanese adolescents and adults aged 14-94, which found higher BMI associated with elevated IOP regardless of age, sex, and blood pressure [39]. Other studies investigated a potential link between the presence of open-angle glaucoma and BMI or obesity [40,41]. In contrast, in a case-control study, no difference in BMI status was found in individuals with and without glaucoma [42].

IOP might get influenced by the haemodynamic system, autonomic nervous system and stage of sleep. [43]. SDB can affect these factors through changes in sleep architecture and an increase in blood pressure and sympathetic tone. The earlier studies conducted on glaucoma prevalence in OSAS reported a significant association between AHI and IOP. [10,44,45] A study reported that an increase in IOP during lying can result in the development or progression of glaucoma in OSA patients [46]. But others found no correlation between IOP and RDI [28].

The change in pharyngeal size and shape due to obesity contributes to SDB. Fat storage in the neck may be particularly associated with risk for SDB, though a subset of patients with SDB are of normal body weight and have a family history of snoring or SDB. Factors affecting upper-airway size or patency include various anatomical variants and abnormalities like nasal obstruction, macroglossia, retrognathia, obesity, alcohol or sedative intake and body position during sleep. We found large neck circumference in 103 male patients, and 93 out of 110 patients in the POAG group with ESS > 10 had neck girth > 42 cms. Also, the male population in the study group had high blood pressure with more ENT problems (Table 4). Moreover, the incidence of these parameters was highly significant (P-value < 0.001) in the POAG group with SDB (ESS > 10, Table 6). Various clinical and epidemiological factors associated with sleep-disordered breathing like increasing age, male sex, large neck circumference, obesity and reported snoring with daytime sleepiness were similar to previous studies [7,47,48]. These co-morbidities are also risk factors for glaucoma and may contribute to our finding of a higher prevalence of glaucoma in the SDB group [49]. In the first half of the 1980s, a relationship was proposed between snoring, sleep apnoea and hypertension, initially supported by epidemiological studies that used self-reported snoring as a marker for sleep apnoea [50,51] and later, a correlation between sleep apnoea and increased cardiovascular risk was suggested [52]. Strong associations with systemic hypertension had been reported in glaucoma patients. [53,54] It is also reported that in the presence of other vascular risk factors, the optic nerve head blood flow may be reduced below a critical level due to physiological nocturnal hypotension and hence play a role in the pathogenesis of anterior ischemic optic neuropathy and glaucoma. [55].

On the other hand, SDB due to large swings in nocturnal blood pressure [56] and recurrent severe hypoxia [57] may aggravate anoxic optic nerve damage, which is implicated in glaucoma. Hence, various studies suggested that patients with OSA are at significant risk of developing primary open-angle glaucoma (POAG) and vice versa. [9,10,12,19].

The limitation of our study is the use of a subjective method in the form of a questionnaire instead of objective measurement to determine the presence of sleep-disordered breathing in a group of 400 patients. We found an association between primary open-angle glaucoma (POAG) and sleep-disordered breathing (SDB), but the reciprocal relationship between SDB and glaucoma could not be established.

Conclusion

A multidisciplinary approach that coordinates input from diverse behavioural, medical, surgical, otolaryngologist and, above all, the ophthalmologist would be of value in complex assessment and therapy for POAG and SDB. Moreover, the influence of SDB in the prevalence, incidence, and development of glaucoma is unknown compared with other potentially modifiable risk factors. [9-16,19,20,24] Earlier, Marcus et al [12] studied sleep disorders as a risk factor for normal-tension glaucoma and Boland et al recently conducted a detailed evaluation of factors contributing to the development of glaucoma and found sleep apnea to be one of the risk factors.[58]. Hence, there is a need and scope for further studies to evaluate the risk of SDB in glaucoma.

What does this study add to the existing knowledge?

An early detection, increased community awareness, appropriate treatment, and patient's compliance with treatment may slow down the progression of optic nerve head damage. Hence, we highly recommend that a sleep history from patients with POAG and vice versa be incorporated in a routine examination.

Contribution details

Dr Inderjit Kaur has conceptualized the study, prepared, verified all the drafts and approved the final draft.

Late **Dr Geetwinder Kaur** designed the study protocol, conducted the ophthalmological examination and data collection. **Dr Mandeep Kaur** has done the manuscript writing. **Dr Jagdeepak Singh** has done the ENT examination of all patients and, along with **Dr Inderjit Kaur**, have provided vital inputs and supported the study.

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