

Sleep Apnea and Idiopathic Leg Edema: A Case Control Study

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Abstract- Idiopathic leg edema is subject to a lot of debates among physicians. Recently sleep apnea was stated to be the cause. We sought to investigate this matter in a sample of Iranian patients with idiopathic leg edema. In this case-control study, 110 patients were selected based on our inclusion/exclusion criteria and allocated to the case (with idiopathic edema, n=55) and control (without edema, n=55) groups. Sex, age, weight, height, and body mass index (BMI) of all subjects were recorded. We evaluated daytime somnolence of all patients using Epworth sleepiness scale and then calculated Apnea, hypopnea index (AHI) using ResMed ApneaLink and $AHI \geq 15$ were considered as sleep apnea. Age and sex of both groups were not significantly different. Cases had higher BMI than control groups ($P=0.03$), but they were not significantly different for obesity ($P=0.197$). AHI was significantly higher in cases (17.85 ± 24.31 vs. 9 ± 7.37 $P=0.012$). Daytime somnolence (cases 8.18 ± 5.3 vs. controls 6.5 ± 3.3) was also higher in cases. Overall Odds ratio of leg edema and sleep apnea was 3.068 ($P=0.025$), but it wasn't significant in the two genders. Idiopathic bilateral leg edema is strongly associated with sleep apnea. Routine sleep apnea assessment in patients with idiopathic bilateral leg edema is recommended for both genders.

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Introduction

Edema is frequently accompanied by sleep apnea, and when edema occurs, it is usually attributed to obesity, abnormal pulmonary function, pulmonary hypertension and cor pulmonale (1-4). RP Blank field *et al.*, conducted a series of cross sectional studies in which they proposed that cardiac causes of leg edema are more important than previously perceived. Further, they reported that sleep apnea is responsible for higher pulmonary artery pressure and right heart function disorder in patients with edema. They finally concluded that sleep apnea is a major cause of idiopathic leg edema in women independent of obesity (5-7). As their sample size was small and their groups lacked proper standardization and because their team is the only one to research on this matter, we conducted this research to further clarify if the association of idiopathic bilateral leg edema and sleep apnea exists.

Materials and Methods

This was a case control study in which the two groups consisted of 55 patients. Single physician (R.S) enrolled the patients consecutively from October 2010 until March 2014 in a single urban heart center. Inclusion criteria for patient enrollment were: age >18, normal left heart ejection fraction ($EF \geq 50\%$). Exclusion criteria were: uncontrolled asthma or chronic obstructive pulmonary disease ($FEV1 < 80$), Restrictive pulmonary disease, hypoalbuminemia (albumin <2 gr/dl) or proteinuria ($300 \leq$ mg/dl), pregnancy, untreated hypothyroidism, valvular heart disease, congenital heart disease, diastolic heart failure, use of dihydropyridine calcium channel blockers, use of narcotics or drug abuse, unilateral nonpitting edema, involvement of lower extremity fingers, idiopathic cyclic edema and pelvic malignancy. This study was approved by local ethics committee. All the eligible patients agreed to participate and were free to leave the study at their will. Pulmonary artery pressure of all our subjects was recorded after they first underwent echocardiography. Patients with idiopathic leg edema (≥ 1 and more or ≥ 1 mm pitting) who adhered to our inclusion/exclusion criteria were enrolled in the case

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group and those without leg edema were allocated to control group. We formed a data sheet in which we recorded age, sex, weight, height, body mass index (BMI) and socioeconomic status for each participant. The two groups were matched for age, sex and socioeconomic status at this stage. Participants underwent echocardiography for assessment of pulmonary artery pressure. Then they filled Epworth's Sleepiness Scale (ESS). This scale measures sleepiness in 8 different daytime activities and scales each from 0 to 3. Scores of ≥ 10 show poor sleep quality (8,9)

All participants were evaluated for sleep apnea using ResMed ApneaLink Ox™ in at least 8 hours sleep time at home. Decrease in airflow by 80% of baseline for at least 10 seconds was called an apnea episode and 30% decrease in baseline airflow plus oxygen desaturation of ≥ 3 or 4% was called hypopnea episode. The accuracy of diagnosing sleep apnea with this device was comparable with polysomnography (10). The sum of apnea and hypopnea episodes per hour was called Apnea/hypopnea index (AHI). $AHI \geq 15$ was diagnosed with sleep apnea.

Mean values between case and control groups were compared with student's *t*-test, and chi square statistics were used to compare differences between proportions. Logistic regression analysis was used to test for presumed associations between leg edema and sleep apnea.

Results

One hundred and ten subjects enrolled in the study, 55 with and 55 without edema. In control group, there were 30(54.5%) males and 25(45.5%) females while it was 33(60%) males and 22(40%) females in the case group. Two groups were not significantly different for sex distribution. ($P=0.56$)

Mean \pm SD age was 54.89 ± 11.71 for control, and 56.8 ± 10.9 for case group and the groups were not statistically different. ($P=0.38$)

In-group analysis of cases showed that men were significantly younger than women. (52.21 ± 9.8 versus 63.68 ± 8.93 , $P < 0.001$)

Compared to controls, cases had higher BMI (24.5 ± 3.2 versus 23.3 ± 2.34 , $P=0.03$), higher AHI (17.85 ± 24.31 versus 9 ± 7.37 , $P=0.012$) and were more sleepy (ESS scores 8.18 ± 5.3 versus 6.5 ± 3.13 , $P=0.022$).

Categorizing BMI as normal (BMI $<$ 25), overweight (BMI=25-30), obese (BMI $>$ 30), the two groups were not significantly different ($P=0.197$).

Cases and controls were not significantly different for mean \pm SD pulmonary artery pressure. (27.21 ± 3.26 in cases and 26.66 ± 4.12 in controls, $P=0.185$)

AHI scores for genders are listed in table 1.

Table 1. Mean \pm SD AHI scores for sexes

	Sex	Case	Control	P
AHI	male	22.1 \pm 29.30	11.2 \pm 8.64	0.047*
	female	11.40 \pm 11.79	6.36 \pm 4.31	0.069

* $P < 0.05$

Categorizing apnea to moderate (AHI= 15-34) and severe (AHI $>$ 34), cases had more severe apnea than

controls. (Table 2).

Table 2. Sleep Apnea severity comparison in case and control groups

Apnea severity	Case	Control	P
moderate	10	6	0.036*
severe	7	1	

* $P < 0.05$

Logistic regression analysis of both groups is shown in Table 3.

Sleep apnea was associated with idiopathic leg edema

regardless of sex ($P=0.025$), and there was a trend toward women being more susceptible for this association than men, but it was not statistically significant.

Table 3. Logistic regression Analysis for sleep apnea and idiopathic leg edema association

Variable	Coefficient	Wald	P	Odds ratio
Total sample(N=110) Apnea status	1.121	5.049	0.025*	3.068
Women(N=47) Apnea status	1.674	2.080	0.149	5.333
Men(N=63) Apnea status	0.956	2.723	0.099	2.6

*P<0.05

Discussion

Our study was the first to assess the association between sleep apnea and idiopathic leg edema, in Iran. Our results showed that there is a strong association between sleep apnea and idiopathic leg edema regardless of sex with a trend toward women. Also, we found that Men are more prone to this association in younger ages. In our study, there were no significant differences between the two groups for pulmonary artery pressure. This suggests that if the edema develops as the result of increase in pulmonary artery pressure, it would be temporary or during sleep.

Blankfield's team is believed to be only to work on this association in their studies (5-7,11). In a cross sectional study, he compared obese patients with and without idiopathic leg edema for the prevalence of obstructive sleep apnea and found this association in women rather than men (7) although there are similarities, our study is different in design and methods used. We used a case control design for our study and cared to standardize the groups for sex and age. We also tried to have a bigger sample size. On the other hand, we didn't limit our selection among obese patients, and although our case group had higher BMI, they weren't more obese than controls. This is why BMI in our study is a lot lower than Blankfield's (24.98±3.57 versus 47±9.3). Our sample specifics could be a better match for the overall population.

The overall odds ratio from our study (3.068) and Blankfield's (2.8) are close. But we failed to demonstrate any difference in association relative to genders in our groups. This difference would be due to the impact of obesity in Blankfield's study. Although he stated that the odds ratio is regardless of obesity, it might influence the sample size needed to demonstrate a meaningful association. So, although we used bigger sample size, our results would be subject to type 2 error.

sleep apnea and idiopathic leg edema are heavily correlated, and this correlation is regardless of sexes.

Although there is a trend toward women being more involved, Men seem to get involved in younger ages. Sleep apnea assessment is recommended in approach to idiopathic leg edema in all patients.

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