ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Research Article

Effects of Continous Positive Airway Pressure Treatment on Microalbuminuria in Obstructive Sleep Apnea: A Pilot Study

Pius Ochieng[1,2], Manideep Dutulluri[1], Frank Genese Do[1], Zina Nazan Lpn[2], Edward Eden[1,2] and Raymonde Jean[1,2]

[1]Department of Medicine, Mount Sinai St. Luke's and Mount Sinai Roosevelt, Icahn School of Medicine at Mount Sinai, New York

[2]Division of Pulmonary and Critical Care Medicine, Mount Sinai St. Luke's and Mount Sinai Roosevelt, Icahn School of Medicine at Mount Sinai, New York

***Corresponding Author:** Raymonde Jean, Mount Sinai St. Luke's and Mount Sinai Roosevelt, Icahn School of Medicine at Mount Sinai, New York.

Received: October 29, 2016; **Published:** November 09, 2016

Abstract

Background: Obstructive sleep apnea (OSA) is a common disorder that is associated with various cardiovascular conditions. Treatment of OSA with Continuous Positive Airway Pressure (CPAP) is postulated to positively mitigate cardiovascular disorders. Microalbuminuria is well established as an early marker of cardiovascular disease, and it can be assessed by albumin to creatinine ratio.

Objectives: We documented the baseline prevalence of microalbuminuria in OSA patients being started on CPAP and correlated it with various findings of nocturnal polysomnograms (including Apnea- hypopnea index/AHI and sleep time with oxygen saturation below 90%/T sat < 90%). For patients with significant microalbuminuria; we repeated the urine testing after 3-12 months, and correlated changes with CPAP compliance.

Material and Methods: This was a prospective longitudinal pilot study of 32 adult patients with OSA being started on CPAP therapy. Exclusion criteria included renal disease, diabetes and those recently started on angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or statins. Baseline sleep study data was extracted and spot urine was tested for albumin-creatinine ratio. Follow up urine studies were performed for microalbuminuria at 3 - 12 months and CPAP compliance data was collected. Significant microalbuminuria defined as level greater than 20 mg/dl.

Results: Of forty-nine patients screened over 18 months, 17 met the exclusion criteria and 32 were analyzed. Sixteen (50%) were male with a mean age of 51.2 years (range 29 - 74), and 10 (31%) had severe OSA. All patients had some degree of microalbuminuria (range 3.2 - 138.6 mg/dl) and 10 (31.3%) had significant microalbuminuria. T sat < 90%, AHI, age and gender did not correlate with microalbuminuria (p values 0.13, 0.57, 0.14 and 0.87 respectively). Seven out of ten (70%) with significant microalbuminuria had follow up urine testing which showed improvement over previous baseline values in five (71.4%) and worsening in two (28.6%). Improvement in albuminuria was significantly associated with CPAP adherence (p value < 0.05).

Conclusion: OSA may be associated with a high incidence of microalbuminuria. However, no clear predictors were identified for microalbuminuria in our patient cohort. CPAP therapy and adherence may be associated with improvement of microalbuminuria.

Keywords: *Microalbuminuria; Obstructive Sleep Apnea; Albuminuria; cardiovascular disease; albumin-creatinine*

Introduction

The exact prevalence of obstructive sleep apnea (OSA) is unknown, but it has been reported in up 24% of men and 9 % of women in some populations. Its prevalence increases with age, and OSA may affect more than 50 - 65% of individuals over the age of 65 [1]. OSA has been associated with various cardiovascular diseases (CVD) including systemic hypertension, congestive heart failure (CHF), stroke and arrhythmias without clear causality [2]. However, studies have increasingly suggested that OSA itself may lead to or worsen cardiovascular disease.

Albuminuria is an established early marker of cardiovascular disease [3]. Numerous epidemiologic and experimental studies have established that microalbuminuria is associated with an increased risk for all-cause and cardiovascular mortality, cardiac abnormalities, cerebrovascular disease, and, possibly, peripheral arterial disease [4].

Albuminuria is a direct manifestation of renal vascular bed (glomerular) involvement and also reflects subclinical vascular damage in all vascular beds [4]. Albuminuria can be easily and reliably quantified by a spot urine albumin-creatinine ratio. A ratio of less than 30 mg/g creatinine is considered normal; between 30 to 300 mg/g creatinine is micro-albuminuria and above that, macro-albuminuria. The correlation with CVD is observed even at levels of albuminuria below the conventional threshold for albuminuria, and many studies use a ratio of 20 mg/g creatinine as the threshold for abnormal value [5]. Periodic screening for albuminuria allows for the early identification of systemic vascular disease, and its resolution by a multifactorial intervention strategy may potentially reflect the mitigation of systemic vascular damage [4].

Studies have shown mixed results regarding the association between OSA and albuminuria, with some showing a positive association and others showing no association [6,7]. To our knowledge, the resolution of CVD-related markers with treatment of OSA with CPAP is not documented. This study is designed to assess if continuous positive airway pressure (CPAP), which is the current standard therapy for OSA, reverses or improves albuminuria.

Objective

To investigate the impact of OSA treatment and microalbuminuria, we first sought to document spot urine albumin/creatinine ratio in patients diagnosed with OSA and starting on CPAP treatment at therapy initiation (baseline) and 3 through 12-month follow-up visits. For those with significant microalbuminuria, we then sought to correlate changes in the urine- creatinine ratio with CPAP use.

Materials and Methods

The investigators consecutively screened all newly diagnosed OSA patients being evaluated for CPAP therapy between August 2013 and February 2015 at St Luke's and Roosevelt Hospitals, New York. For patients who consented to participation in the study, demographic information, medical history, medication list and laboratory values were obtained by interview and review of the patient's electronic medical record.

Patients were excluded if they had documented renal failure with glomerular filtration rate (GFR) less than 90 within 3 months of recruitment, nephrotic syndrome, diabetes mellitus, recent (within 1 year) initiation of angiotensin-converting enzyme inhibitor(ACEI) or angiotensin receptor blocker (ARB) therapy, or were pregnant.

Baseline and follow-up spot urine albumin-creatinine ratios were collected at the time of clinic visit. Follow-up urine albumin-creatinine ratios were measured at 3 - 12 months while on CPAP treatment during regular follow up clinic visits. A urine pregnancy test was also performed at the same scheduled visits on female participants. The urine albumin and creatinine was measured using the Vitros 950 automated protein and creatinine analyzer (Johnson and Johnson). Albumin-creatinine ratios were calculated and used to estimate daily urine albumin excretion. Significant albuminuria was defined as an albumin/creatinine ratio greater than 20mg/g. Changes in the level of

albuminuria were correlated with CPAP compliance as the primary outcome measure of interest for the study.

Baseline albumin-creatinine ratio at recruitment was also correlated with severity of OSA (mild AHI < 15, Moderate AHI 15 - 30 or severe AHI > 30) and total time of oxygen saturation of less than 90% (T-Sat < 90%) as documented in the diagnostic sleep study.

CPAP compliance was defined using the Medicare definition of CPAP for at least 70% of the time and at least 4 hours per night. Compliance was analyzed as a categorical variable either as adherent, or non-adherent, or also as a continuous variable using percentage sleep time of CPAP use. Adherence was assessed objectively by reviewing the CPAP machine monitoring chips, which monitor and document the use of the device for up to 3 months, or through the online reported statistics available from the CPAP providing company. The study was approved by the Mount Sinai St Luke's and Mount Sinai Roosevelt Hospital internal review board.

Data Analysis

Data analysis was performed using GraphPad Prism Software (Version 5, GraphPad Software, Inc., La Jolla, CA). Baseline prevalence of albuminuria was reported as a proportion. Descriptive data was presented as means with standard deviation (SD) for normally distributed data, and as medians for non-normally distributed data. Differences in microalbumin level before and after CPAP treatment was compared by two-way analysis of variance (ANOVA). Pairs of groups (with and without clinically significant albuminuria) were compared by two tailed Student's t-test. For all statistical tests, significance was defined using an α-value of 0.05. Changes in albuminuria were correlated with CPAP compliance using Mann-Whitney U test. Compliance with CPAP was analyzed both as a categorical (either as compliant if met Medicare definition or not if did not meet this definition) and continuous (based on percentage of time when CPAP was used) variable.

Results

Forty-nine patients with newly diagnosed OSA were screened over 18 months, out of whom 17 met the exclusion criteria. Of those excluded, 13 had diabetes, 2 had been started on ACEIs in the preceding year, and 2 had chronic kidney disease.

The baseline characteristics of the 32 analyzed are illustrated in Table 1. Sixteen (50%) were male, the mean age was 51.2 years (range 29 - 74), and 10 (31%) had severe OSA. Eleven had hypertension, but only 2 of those had elevated blood pressure during the initial office visit, while the other 9 had controlled blood pressure. One patient had a history of systolic CHF which was not decompensated. Sixty-nine percent had an oxygen saturation drop below 90% on sleep study.

Parameter	Value
Age	Mean 51.2 (Range 29-74)
Gender	16 Male (50%)
HTN	11 (34%) but only 2 uncontrolled
BMI	Mean 36.8 (Range 21.6-81.4)
MACE	1 (3.1%)- CHF
AHI > 30 (Severe OSA)	15 (47%)
AHI 15 - 30 (Moderate OSA)	7 (22%)
AHI < 15 (Mild OSA)	10 (31%)
T sat < 90%	22 (69%)

Table 1: *Baseline Characteristics of the study subjects.*

Key: *HTN- hypertension, BMI- Body mass index, MACE- Major Adverse Cardiovascular Event, CHF- Congestive Heart Failure, AHI- Apnea Hypopnea Index, T Sat 90- Time period with oxygen saturation less than 90% on polysomnography.*

All 32 patients had some degree of microalbuminuria (range 3.2 - 138.6 mg/dl) but 10 (31.3%) had clinically-significant microalbuminuria defined as urine albumin-creatinine ratio greater than 20 mg/g. Of the 10 with microalbuminuria, 2 had values in the range of 20 - 30 mg/g, 3 in the range of 30 - 40 mg/g, 3 in the range of 50 - 60 mg/g, 1 in the 70 - 80 mg/g range and one slightly above 130 mg/g. Notably, the GFR remained stable for all of them 32 patients.

Analyzing all the 32 subjects, various sleep study and biometric parameters including T sat < 90%, AHI, age and gender did not correlate with microalbuminuria as illustrated in Table 2. Owing to the small sample size, the range of the confidence Interval was also very broad. Of the 10 with significant microalbuminuria, 7 (70%) had follow-up urine testing and 3 were lost to follow up. Resolution of significant microalbuminuria was noted in five (71.4%) of the seven, and persistence of significant microalbuminuria was observed in two (28.6%). The follow-up testing was done at 3 months for 2 and in 6 months for 2 subjects. All patients with resolved microalbuminuria fit the definition of CPAP adherence, and none of the two who has persistent microalbuminuria were adherent to CPAP therapy. CPAP adherence was significantly associated with improvement in albuminuria ($p < 0.05$).

Parameter	P Value
Age	0.171 (95% CI -2.16- 11.63)
Gender	0.190 (95% CI -6.95- 33.41)
AHI	0.654 (95% CI -26.48- 16.89)
T sat < 90%	0.330 (95% CI -9.52- 3.31)
Nadir Oxygen Saturation	0.818 (95% CI -8.45- 10.55)
RDI	0.556 (95% CI -35.16- 19.47)
BMI	0.625 (95% CI -8.16- 13.32)

Table 2: *Correlation of degree of microalbuminuria with various biometric and polysomnographic parameters.*

Key: *AHI- Apnea Hypopnia Index, T sat<90- Time period with oxygen saturation less than 90%, RDI- Respiratory disturbance Index, BMI- Body mass Index.*

Discussion

The prevalence of significant microalbuminuria (31.3%) is considerably higher than in previous reports. Casseley reported a prevalence of 5.4%, and none of Catalan's subjects had microalbuminuria [6,8]. The populations studied are different, and our city population may have more albuminuria due to genetic or environmental reasons.

Unlike Faulx., *et al*. we did not find a correlation between AHI and microalbuminuria [10]. This may be due differences in comorbidities in the study populations and the different analytical methods applied. Similar to our findings, Casserly and Agrawal did not find a correlation between AHI and microalbuminuria [6,11]. Unlike Casserly., *et al*. we did not find a correlation between a diagnosis of hypertension and BMI with microalbuminuria. This may be explained by the fact that all except two of our hypertensive patients had controlled blood pressure. Furthermore, our stringent exclusion criteria may have further limited confounder for the microalbuminuria.

We conclude that microalbuminuria which is a manifestation of endothelial dysfunction is complex and cannot be simply predicted by polysomnography and biometric parameters. Endothelial dysfunction is a complex process involving the regulation of hemostasis and fibrinolysis, vasomotor activity, permeability to macromolecules, leukocyte adhesion, vascular smooth muscle cell proliferation, nitric oxide dysregulation, and numerous other processes, and therefore it is possible that these simple parameters do not adequately predict the evolution or manifestation of this process.

Improvement or resolution of significant microalbuminuria seems to correlate with CPAP adherence both as a categorical and continuous variable. Although our study demonstrated that the 5 who were adherent showed improvement while the 2 who were non-adherent

did not, this is too small a sample to draw firm conclusions. It however raises a very interesting observation which, if confirmed by a larger study, may provide further impetus to push for CPAP adherence. It is very conceivable that OSA treatment positively mitigates endothelial dysfunction as illustrated by Chan., *et al*. in a pediatric population treated with adenotonsillectomy using an ultrasonographic assessment of endothelium-dependent flow-mediated dilation (FMD) of the brachial artery [12].

Study Limitations

There are some limitations to the conclusions found in our study. First, the small sample size of 7 patients limits the generalizability of this single center study. Ultimately 7 or the 32 patients recruited (21.9%) were able to be fully followed, and as such a larger multicenter study may be necessary to further study these effects. Furthermore, the interval collection of follow-up urine samples over a long-time period (3 - 12 months) offers no insight on the exact time-point during which changes in microalbuminuria occurred. It is also not clear from the study whether this improvement in microalbuminuria is sustained beyond a year. Another limitation is that albuminuria is a very non-specific diagnostic measure, due to many confounding co-morbidities such as diabetes, kidney failure and obesity. Despite excluding patients with diabetes and renal failure, the study may still be limited in showing clear association between albuminuria and OSA. In spite of this limitation, obesity as an entity did not correlate to degree of microalbuminuria as illustrated in Figure II. Similarly, there may be other cofounding medical conditions which were not adjusted for in our study. Although we did exclude patients with kidney disease, nephrotic syndrome, and those using ACEI and ARB medications, it is likely that other cardiovascular or metabolic conditions may be present which would also impact albuminuria. Further investigation may be necessary to fully account for clinical factors which affect albuminuria.

Bibliography

1. Carmen M Schröder and Ruth O'Hara. "Depression and Obstructive Sleep Apnea (OSA)". *Annals of General Psychiatry* 4 (2005): 13.
2. Bradley TD and Floras JS. "Obstructive sleep apnea and its cardiovascular consequences". *Lancet* 373.9657 (2009): 82-93.
3. Tagle R., *et al*. "Microalbuminuria- is it a valid predictor of cardiovascular risk". *Cleveland Clinic Journal* 70.3 (2003): 255-261.
4. Weir MR. "Microalbuminuria and Cardiovascular disease". *Clinical Journal of the American Society of Nephrology* 2.3 (2007): 581-590.
5. Arnjoy J., *et al*. "Low grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The Framingham Heart Study". *Circulation* 112.7 (2005): 969-975.
6. Casserly LF., *et al*. "Proteinuria in obstructive sleep apnea". *Kidney International* 60.4 (2001): 1484-1489.
7. Comondore VR., *et al*. "The Impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with OSA- A pilot feasibility Randomized crossover trial". *Lung* 187.1 (2009): 17-22.
8. J Sayas Catalán., *et al*. "Proteinuria in Obstructive sleep apnea". *Kidney International* 61.4 (2002): 1551.
9. Chaudhary BA., *et al*. "Sleep apnea, proteinuria, and nephrotic syndrome". *Sleep* 11 (1988): 69-74.
10. Faulx MD., *et al*. "Obstructive sleep apnea is associated with increased urinary albumin excretion". *Sleep* 30.7 (2007): 923-929.
11. Agrawal., *et al*. "Albuminuria and renal function in obese patients evaluated for Obstructive Sleep Apnea". *Nephron Clinical Practice* 113.3 (2009): c140-c147.
12. Kate C Chan., *et al*. "Endothelial Function in Children with OSA and the Effects of Adenotonsillectomy". *Chest* 147.1 (2015): 132- 139.

Volume 2 Issue 4 November 2016