

Prevalence of Obstructive Sleep Apnea in Patients with Chronic Wounds

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Study Objectives: Chronic non-healing wounds are a major human and economic burden. Obstructive sleep apnea (OSA) is prevalent in patients with obesity, diabetes, aging, and cardiovascular disease, all of which are risk factors for chronic wounds. We hypothesized that OSA would have more prevalence in patients of a wound center than the general middle-aged population.

Methods: Consecutive patients of the Ohio State University Comprehensive Wound Center (CWC) were surveyed with the Berlin and Epworth questionnaires. In the second stage of the protocol, 50 consecutive unselected CWC patients with lower extremity wounds underwent home sleep studies.

Results: In 249 patients of the CWC who underwent the survey study, OSA had been previously diagnosed in only 22%. The prevalence of high-risk status based on questionnaires for OSA was 46% (95% CI 40%, 52%). In the 50 patients who underwent

home sleep studies, and using an apnea hypopnea index of 15 events per hour, the prevalence of OSA was 57% (95% CI 42%, 71%). There was no difference between the Berlin questionnaire score and weight between patients with OSA and those without.

Conclusions: The prevalence of OSA in patients with chronic wounds exceeds the estimated prevalence of OSA in the general middle aged population. This study identifies a previously unrecognized population with high risk for OSA. Commonly used questionnaires were not sufficiently sensitive for the detection of high risk status for OSA in this patient population.

Keywords: Obstructive sleep apnea, chronic non-healing wound

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Chronic non-healing wounds are a major health problem with steadily increasing importance.¹ The prevalence of chronic leg ulcers is 3%–5% in the population over 65 years of age, with an increase of up to 12% in the population over 70 years of age.² The most prevalent forms of chronic wounds are leg ulcers caused by chronic venous insufficiency (CVI)^{3–6} accounting for 70%–90% of ulcers found on the lower leg,⁷ followed by diabetic foot ulcers.⁸ Despite significant advances in knowledge, management of chronic wounds continues to involve frequent visits to wound centers and repeated interventions imposing significant burden on patients and society.^{3,9,10} Chronic wound ulcers are commonly associated with delayed healing requiring an average of 4–6 months, with a substantial number of patients failing to heal.^{11,12} The burden of chronic wounds is expected to be increasing in coming years with the increased aging and obesity of the population.²

Obstructive sleep apnea (OSA) is a disorder of intermittent hypoxia^{13–18} and severe vascular complications including hypertension, coronary disease, and stroke.^{19–22} OSA is present in 5%–10% of the middle-aged population and probably increasing in incidence due to the increasing obesity and age of the population.²³ These are also the risk factors of chronic non-healing wounds.² Therefore, it is very likely that patients with chronic wounds would have higher prevalence of OSA than the general population. We endeavored to characterize the risk factors for OSA in patients of academic wound center and to determine the actual prevalence of OSA in this population.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Patients with non-healing wounds have high prevalence of cardiovascular disease and significant rate of healing failure. The prevalence of obstructive sleep apnea is unknown in this population.

Study Impact: The study identifies a new population with very high pre-test probability for obstructive sleep apnea. Wound healing in this population may stand to benefit from expedited surveillance and treatment strategies for OSA.

METHODS

The study was conducted at the Ohio State University Comprehensive Wound Center (CWC) in 2 stages. The first stage aimed at characterizing the population of the wound center with questionnaires and demographics. For this stage we targeted consecutive patients of the CWC between October 2008 and September 2009. In the second stage of the study (April 2009 to September 2009), we targeted patients with new lower extremity non-healing wounds with home sleep studies and questionnaires.

Questionnaires

We administered the Berlin questionnaire and the Epworth sleepiness scale to all participants. The Berlin questionnaire is widely used for the prediction of OSA. It has a reported sensitivity of 0.86 and specificity of 0.77 in the general population.²⁴

Table 1—Characteristics of patients of the CWC (n = 249)

Variable	Mean	95% CI
Age (years)	55	53, 57
Berlin positive (%)	46	40, 52
Epworth score	8.9	8.3, 9.5
BMI (kg/m ²)	32	31, 34
Diabetes (%)	42	36, 48
Sex-female (%)	52	46, 58

BMI refers to body mass index

Table 2—Comparison between all patients with chronic wounds with positive and negative Berlin questionnaire (n = 249)

Variable	Positive (n = 115)	Negative (n = 124)	Difference	95% CI for Difference
Age (years)	52	58	-6	-2, -9
Epworth score	11	7	4	2, 5
BMI (kg/m ²)	37	28	8	6, 11
Diabetes (%)	57	31	26	14, 38
*Sex-female (%)	54	49	-5	-17, 8

*indicates the only relationship not significantly different; BMI, body mass index

The questionnaires were given to all patients by the clinic staff without prior screening, consideration of existing symptoms, or knowledge of location or type of wounds.

Home Sleep Studies

Participants consented and underwent an in-home type 3 cardiorespiratory sleep study (Stardust II, Respironics Inc, PA), which records flow, oxygen saturation, effort, position, and heart rate. This method of testing is validated and accepted for the diagnosis of OSA.²⁵

We provided home sleep studies to consented patients who presented to the CWC with a new lower extremity wound on two separate days (Monday and Thursday) weekly between April and September of 2009. These participants were a portion of the total population who completed the questionnaire portion of the study. There was no prior screening for symptoms or risk factors of sleep apnea.

The Ohio State University Institutional Review Board approved the study protocol (2007H0242). The study was registered in the national clinical trial registry (NCT00679757).

Analysis and Sleep Study Scoring

For sleep study interpretation, we defined OSA as an apnea hypopnea index (AHI) ≥ 15 events per hour. Apnea was scored when complete or near-complete ($< 10\%$ of baseline flow) cessation of flow occurred. Hypopnea was scored when a 50% reduction in the flow signal occurred in association with 4% desaturation. Duration of 10 seconds was required for all events.

Descriptive statistics, such as frequencies and percentages and their confidence interval or standard error, were used to characterize the subjects and to report the prevalence and type

of OSA in the study population. Comparisons on a profile of patient characteristics were used to understand the differences between OSA and non-OSA wound patients. A student *t*-test was used for the comparison of characteristics between the 2 groups.

RESULTS

Characteristics of Patients of the Comprehensive Wound Center

Two hundred and forty nine patients with chronic wounds returned the questionnaires. **Table 1** lists the characteristics of the wound center patients who participated in the questionnaire study. Of note, the prevalence of high-risk status for OSA, defined by a positive Berlin questionnaire, was 46% (95% CI 40%, 52%). OSA was already diagnosed in only 22% of patients in this cohort. **Table 2** lists the comparisons between the group with high-risk status (positive Berlin questionnaire) and the group with low-risk status (negative Berlin questionnaire), excluding those previously diagnosed with OSA. Note that patients with high risk for OSA were more likely to have diabetes, and tended to be sleepier based on the Epworth sleepiness scale. Based on the components of the Berlin questionnaire, high-risk patients were more obese and more likely to be hypertensive. Otherwise the 2 groups were similar in most characteristics. This prevalence of risk status of OSA as determined by the Berlin questionnaire exceeds that in the general middle-aged population.²⁶

Prevalence of OSA in Patients with Chronic Lower Extremity Wounds

Fifty patients underwent home sleep studies. Of those, 4 patients had non-interpretable study and 46 had successful sleep recordings, based on adequate recording times for all signals. Using the cut-off for AHI of 15 events per hour, the prevalence of OSA in these patients was 57% (95% CI 42%, 71%). If an AHI cut-off of 5 had been used, the prevalence of OSA in this population would have been 82% (38/46). **Table 3** lists the comparisons between patients with OSA and those without. Note that patients with OSA were not different in body mass index from those without OSA. Also, patients with OSA were not more likely to have positive Berlin questionnaire. OSA patients were more likely to have hypertension (69% versus 25% [95% CI 17%, 72%]) than those without OSA.

The sensitivity of Berlin questionnaires compared to the ambulatory sleep testing was 0.58 and the specificity was 0.44. The positive predictive value of this questionnaire was 0.63 and the negative predictive value was 0.39 in this population. Using the AHI > 5 cut off, we found similar pattern with no significant differences in the same variables listed in **Table 3** between the two groups with and without OSA (not reported). In particular, there was no difference in BMI or Berlin score between patients with OSA and patients without OSA. Using a cut-off of 5, the negative predictive value for Berlin questionnaire was 0.06 and the positive predictive value was 0.78.

DISCUSSION

In this study, we evaluated patients with chronic non-healing wounds with Berlin questionnaire and sleep studies. We found the

prevalence of OSA in these patients to be higher than the general middle-aged population (57% vs. 5%-10%, using an AHI cut-off of 15 events/h).²⁶ Compared with the published sensitivity of Berlin questionnaires (0.86)²⁴ in the general population, we found low sensitivity and positive predictive value for this diagnostic tool in this population. We also demonstrated the feasibility of using an ambulatory based testing approach in wound centers.

OSA is a disorder of sympathetic activation,^{27,28} impaired vascular response to hypoxia,^{29,30} and oxidative stress.³¹ Impaired endothelial vasoregulation is an important consequence of OSA³² and results in impaired vascular response to hypoxia.^{29,33} The intermittent hypoxia and impaired endothelial vascular control in OSA are likely to compromise perfusion and delay healing in patients with chronic wounds. Additionally, OSA is associated with oxidative stress and inflammation, both of which are critical factors in wound non-healing.^{34,35} Several mechanisms have been proposed in the pathogenesis of chronic wound ulcers.³⁶ The most important abnormalities that are central to the pathogenesis of chronic wound ulcers include disrupted oxidant to antioxidant capacity balance or oxidative stress,³⁴ decreased perfusion,³⁷ and dysregulated inflammatory response.³⁸ Impaired perfusion of wounds results in decreased oxygen and nutrients delivery to the wound site, and impaired healing.³⁷ All the elements of the pathogenesis of chronic wounds are central components of the pathogenesis of OSA.

We used home sleep studies rather than standard polysomnography for diagnosis of OSA. These devices have been validated against the polysomnography²⁵ and are accepted by the American Academy of Sleep Medicine for the diagnosis of OSA.³⁹ We implemented a more restrictive criterion for OSA, using the 15 events per hour cut-off and may have biased our prevalence conservatively.

This study found that the commonly used questionnaires for OSA screening were not adequately predictive in this population compared to previously reported utility of the Berlin questionnaire.²⁴ In particular, these questionnaires (Berlin and Epworth) cannot be used to determine who should not undergo a sleep study. The high prevalence of OSA and lack of difference in BMI may be explained by the high prevalence of cardiovascular disease in this population. A large percentage of these patients had hypertension and heart failure, both of which are independent risk factors for OSA. The high pretest probability of OSA in this patient population, along with the potential impact of hypoxia on delayed wound healing, justifies a high index of suspicion among clinicians. Chronic wounds and their management continue to be a major health problem. OSA has significant inflammatory and vascular consequences, along with a pattern of intermittent hypoxia, all of which may have a negative impact on wound healing. The role of undiagnosed OSA in the healing failure in patients with chronic wound warrants further evaluation. The identification and treatment of an important comorbidity such as OSA in patients with chronic wounds may result have a positive impact on wound healing. This, however, has to be confirmed in randomized controlled trials.

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Table 3—Comparison between positive and negative OSA patients who underwent HST (n = 46)

Variable	Positive (n = 26)	Negative (n = 20)	Difference	95% CI for Difference
BMI (kg/m ²)	32	33	-2	-7, 4
Hypertension (%)	69	25	44	17, 72
Diabetes (%)	58	50	8	-23, 38
Age (years)	56	49	7	-2, 15
Sex-female (%)	38	70	-32	-61, -2
Minutes < 90	17	1	16	3, 29
Minutes < 85	6	0	6	-2, 14
Minutes < 80	2	0	2	-1, 5
AHI	23	6	17	11, 22
Desaturation index	9	1	8	3, 13
Berlin positive (%)	58	56	1	-31, 34
Epworth score	6.9	7.1	-0.3	-3.8, 3.3

indicates relationships not significantly different

Minutes < 90: time in minutes spent with oxygen saturation below 90%;
Minutes < 85: time in minutes spent with oxygen saturation below 85%;
Minutes < 80: time in minutes spent with oxygen saturation below 80%

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