https://doi.org/10.5664/jcsm.9088

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Association of sleep-disordered breathing and wound healing in patients with diabetic foot ulcers

Lihong Chen, MD[1,*]; Wanxia Ma, MD[1,*]; Naima Covassin, PhD[2]; Dawei Chen, MD[1]; Panpan Zha, MD[1]; Chun Wang, MD[1]; Yun Gao, MD[1]; Weiwei Tang, MD[1]; Fei Lei, BSc[3]; Xiangdong Tang, MD[3]; Xingwu Ran, MD[1]

*[1]Diabetic Foot Care Center, Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, China; [2]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota; [3]Sleep Medicine Center, Mental Health Center, Translational Neuroscience Center, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China; *Contributed equally*

Study Objectives: Sleep-disordered breathing (SDB) is prevalent and associated with an increased risk of morbidity and mortality. However, whether SDB has an adverse impact on wound healing in patients with diabetic foot ulcers (DFUs) is uncertain. The purpose of this study was to investigate the association of SDB with wound healing in patients with DFUs.

Methods: A total of 167 patients with DFUs were enrolled between July 2013 and June 2019 at West China Hospital (Chengdu, China) to assess the association of SDB with wound healing, ulcer recurrence, and all-cause mortality.

Results: Whereas there was no significant association between apnea-hypopnea index (AHI) and wound healing, total sleep time (per hour: hazard ratio [HR], 1.15; 95% confidence interval [CI], 1.01–1.30; $P = .029$), sleep efficiency (per 10%: HR, 1.20; 95% CI, 1.04–1.37; $P = .012$), and wakefulness after sleep onset (per 30 minutes: HR, 0.89; 95% CI, 0.82–0.97; $P = .008$) were associated with wound healing. Total sleep time (per hour: odds ratio, 0.71; 95% CI, 0.51–0.97; $P = .035$) and sleep efficiency (per 10%: odds ratio, 0.68; 95% CI, 0.47–0.97; $P = .033$) were also associated with ulcer recurrence. Mean oxygen saturation (per 3%: HR, 0.68; 95% CI, 0.49–0.94; $P = .021$) and percentage of sleep time with oxygen saturation < 90% (per 10%: HR, 1.25; 95% CI, 1.03–1.53; $P = .026$) were significantly associated with mortality.

Conclusions: SDB is highly prevalent in patients with DFUs but its severity, as conventionally measured by AHI, is not associated with wound healing. Sleep fragmentation and hypoxemia are stronger predictors of poor wound healing, high ulcer recurrence, and increased risk of death in patients with DFUs.

Keywords: diabetic foot ulcer, mortality, polysomnography, sleep-disordered breathing, ulcer recurrence, wound healing

Citation: Chen L, Ma W, Covassin N, et al. Association of sleep-disordered breathing and wound healing in patients with diabetic foot ulcers. *J Clin Sleep Med.* 2021;17(5):909–916.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep-disordered breathing is very prevalent in the diabetes population and is associated with an increased risk of cardiovascular morbidity and mortality. However, whether sleep-disordered breathing has an adverse impact on wound healing in patients with diabetic foot ulcers is uncertain.

Study Impact: This study showed that sleep fragmentation and hypoxemia are strong predictors of poor wound healing, high ulcer recurrence, and increased risk of death, whereas sleep-disordered breathing severity, as measured by AHI, is not associated with outcomes in patients with diabetic foot ulcers. Thus, it is imperative to take sleep-disordered breathing into account and comprehensively evaluate polysomnography to predict wound healing in patients with diabetic foot ulcers.

INTRODUCTION

Diabetic foot ulcers (DFUs) are very common in patients with diabetes mellitus, with lifetime incidence estimated to be between 19% and 34%.[1] DFUs are an important cause of morbidity in these patients, with foot amputation required in up to 20% of patients. DFUs in patients with diabetes are associated with a 2.5-fold greater risk of death compared with the risk in patients with diabetes without foot ulcers, and mortality after diabetes-related amputation exceeds 70% at 5 years for all patients with diabetes.[1] Because of the exorbitant health and economic costs associated with DFUs,[2] this diabetes complication imposes a considerable burden on patients and health care service systems.

Sleep-disordered breathing (SDB) is highly prevalent in the general population. It is estimated that between 711 million and 961 million individuals worldwide have SDB, which is typically defined as an AHI ≥ 5 events/h. Of people with SDB, between 272 million and 458 million have at least moderate to severe SDB (AHI ≥ 15 events/h).[3] People with SDB are more likely to have multiple medical conditions including cardiovascular disease and depression.[4]

SDB is also associated with insulin resistance, impaired glucose metabolism, and obesity.[5] The association between SDB and type 2 diabetes is thought to be bidirectional.[6] SDB is frequent in patients with diabetes, with pooled prevalence estimates of 69% in patients with diabetes.[7] Furthermore,

SDB is associated with an increased risk of complications of diabetes, such as diabetic polyneuropathy and peripheral artery disease.[8,9]

Current evidence indicates that SDB may be implicated in DFU and their consequences. SDB may contribute to ulcer development through an increased risk of diabetic polyneuropathy, peripheral artery disease, impaired glucose metabolism, and obesity.[5,8,9] SDB may also compromise and delay wound healing. In this regard, only a few studies have investigated the impact of SDB on wound healing, yielding inconsistent results. A previous study in people with DFUs showed that probable SDB, as identified from a questionnaire, predicted poor DFU healing as compared to those without SDB (45% vs 20.5%; $P = .025$).[10] On the contrary, Andrews et al found that patients with SDB were significantly more likely to heal within 3 months than patients without SDB (88% vs 59%).[11]

In this prospective cohort study, we evaluated patients with DFUs who were treated using a standard care protocol and underwent polysomnography (PSG) to assess SDB. We sought to (1) investigate the prevalence of SDB in a clinical sample of patients hospitalized with DFUs and (2) investigate the impact of SDB on wound healing and other related complications including foot amputation, wound recurrence, and mortality in patients with DFUs.

METHODS

Patients

This was a prospective, observational cohort study conducted between July 2013 and June 2019 at West China Hospital (Chengdu, China). One hundred sixty-seven patients with DFUs hospitalized in the diabetic foot care center in the department of endocrinology and metabolism were included. Inclusion criteria were age ≥ 18 years and the presence of a foot ulcer. All ulcers corresponded to a Wagner grade between 2 and 4. Exclusion criteria were as follows: hospitalization because of nondiabetic ulcers, such as malignant ulcers, ulcerated tophaceous gout, and ulcers associated with cryoglobulinemia, and active medical diseases (ie, diabetic ketoacidosis, hyperosmolar hyperglycemic state, uncontrolled severe systemic infection, advanced cirrhosis, advanced kidney disease, or refractory psychiatric disease). Patients who were being treated with corticosteroids, immunosuppressive drugs, or chemotherapy were also excluded. No participant had a prior diagnosis of sleep disorders or was being treated for SDB. This study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University, and all participants provided written informed consent.

Procedures

All patients received standard care including pressure offloading, treatment of infection, debridement, local wound care, negative-pressure wound therapy, autologous platelet-rich gel when needed, metabolic control, and treatment of comorbidities and associated risk factors including smoking, hypertension, and dyslipidemia. Current guidelines were followed as per the attending clinician's judgment.[12] Patients with SDB did not receive treatment for this sleep disorder while in the hospital.

Demographics, comorbidities, and laboratory data were obtained from the patient's medical record at the date of admission. Wounds were graded using the Wagner classification. Wound healing was defined as complete epithelial cover. Patients were followed 12 weeks after hospitalization to determine the time to healing and amputation. Mortality and recurrence data were obtained by phone interview of patients or next-of-kin in case of deceased patients during November 2019.

Sleep was assessed using a portable PSG device (Somté, Compumedics, Victoria, Australia). Inpatient PSG was performed 5–7 days after hospitalization in multiple-bed rooms accommodating 2–3 patients at a time. Patients were allowed to sleep based on their habitual sleep time. The apparatus included electroencephalography, bilateral electrooculography, electrocardiography, electromyography (submental and anterior tibialis), nasal pressure and thermal airflow, thoracoabdominal movements, and pulse oxygen saturation. Sleep recordings were scored by certified sleep technologists, who were blind to any diagnosis.

Respiratory events were manually scored according to 2012 American Academy of Sleep Medicine recommendations.[13] Apnea was defined as a drop of at least 90% of airflow from baseline lasting 10 seconds or longer. Hypopnea was defined as a reduced airflow of ≥ 30% from baseline for at least 10 seconds, in association with either a ≥ 3% oxygen desaturation or an arousal. AHI was calculated as the number of apnea and hypopnea events per hour of sleep. SDB severity was graded as follows: normal (AHI < 5 events/h), mild (AHI 5–14.9 events/h), moderate (AHI 15–29.9 events/h), and severe (AHI ≥ 30 events/h). Other PSG variables of interest were total sleep time, sleep efficiency, arousal index, wakefulness after sleep onset (WASO), mean oxygen saturation, oxygen desaturation index, and cumulative nocturnal hypoxemia (percentage of sleep time with oxygen saturation < 90%, T90%).

Statistical analysis

We summarized data as count (%), mean (standard deviation), or median (interquartile range). Between-group comparisons were conducted using an analysis of variance test and a chi-square test, as appropriate. The Kruskal-Wallis test was used for highly skewed continuous data. The association of SDB with wound healing and amputation was assessed over a 12-week period, and wound recurrence and mortality were evaluated over extended follow-up. The Kaplan-Meier method was used to construct curves for wound healing and mortality, using a log-rank test. In this analysis, whereas SDB severity was categorized according to AHI values, the median-split was used for other sleep measures. Unadjusted and adjusted Cox models were used to test whether sleep measures were associated with wound-related outcomes. Multivariable models were corrected for age, sex, body mass index (BMI), wound duration, and Wagner grade. Proportional hazards assumption was verified. Logistic regression was used to assess the association of SDB with amputation and wound recurrence. Statistical analysis was performed with Stata version 13 (StataCorp, College Station, TX), and P values < .05 were considered statistically significant.

Table 1—Baseline characteristics of Patients with DFUs.

	Total (n = 167)	SDB Severity				*P* Value
		Normal (n = 14)	Mild (n = 57)	Moderate (n = 39)	Severe (n = 57)	
Male sex, %	117 (70)	11 (79)	46 (81)	25 (63)	37 (64)	.124
Age, y	64 ± 11	62 ± 11	62 ± 11	63 ± 11	68 ± 10	.003
BMI, kg/m^2	24.6 ± 3.5	23.4 ± 3.4	24.1 ± 3.4	24.5 ± 3.4	25.4 ± 3.5	.014
Smoking, %	97 (58)	11 (79)	37 (65)	21 (54)	28 (49)	.129
Duration of diabetes, y	12.8 ± 7.8	7.4 ± 5.8	11.9 ± 8.4	15.1 ± 6.8	13.4 ± 7.8	.023
HbA1c, %	8.4 ± 2.0	8.3 ± 1.9	8.3 ± 2.4	8.4 ± 1.9	8.4 ± 1.7	.526
Wound duration, mo	2 (1–5)	1 (1–2)	3 (1–6)	2 (1–5)	2 (1–6)	.948
Wound classification						.865
Wagner grade 2	37	3 (21%)	15 (26%)	7 (18%)	12 (21%)	
Wagner grade 3	97	8 (58%)	34 (60%)	22 (56%)	33 (58%)	
Wagner grade 4	33	3 (21%)	8 (14%)	10 (26%)	12 (21%)	
Total sleep time, h	6.0 ± 1.8	6.0 ± 1.7	6.0 ± 1.8	5.9 ± 1.7	6.1 ± 1.9	.867
Sleep latency, min	22.7 ± 26.9	20.5 ± 15.8	26.0 ± 30.5	16.2 ± 13.1	24.3 ± 31.6	.880
Sleep efficiency, %	66.0 ± 16.0	71.8 ± 14.0	65.6 ± 16.5	65.0 ± 14.9	65.6 ± 16.8	.466
WASO, min	132.3 ± 78.8	109.3 ± 69.7	129.3 ± 86.3	150.9 ± 85.3	128.3 ± 67.1	.614
Arousal index, events/h	12.1 (7.9–23.8)	12.3 (5.5–19.3)	10 (6.4–12.1)	12.9 (10–20.7)	19.7 (9.2–38)	< .001
AHI, events/h	24.3 ± 17.2	3.0 ± 1.7	9.1 ± 2.6	22.1 ± 4.6	46.1 ± 17.2	< .001
Oxygen desaturation index, events/h	24.0 ± 19.7	3.8 ± 3.3	10.4 ± 5.9	21.8 ± 8.2	44.3 ± 19.0	< .001
Mean oxygen saturation, %	93.5 ± 3.3	95.0 ± 2.0	94.1 ± 2.6	93.8 ± 2.8	92.4 ± 4.0	.002
T90%, %	14.8 ± 23.4	13.2 ± 24.8	7.5 ± 11.7	12.4 ± 20.6	24.1 ± 30.3	.001

Data are shown as mean (standard deviation), median (quartile), or count (%). BMI = body mass index, HbA1c = hemoglobin A1c, SDB = sleep-disordered breathing, T90%= percentage of time with oxygen saturation < 90%, WASO = wakefulness after sleep onset.

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of our study population categorized according to SDB severity. Overall, the average age was 64 ± 11 years, and 30% of patients were women. The mean duration of diabetes was 12.8 ± 7.8 years, with a mean glycated hemoglobin level of 8.4% ± 2.0%. The median wound duration was 2 months (interquartile range, 1–5 months), with more than half of the patients' wounds classified as Wagner grade 3 (58%) and 20% as Wagner grade 4. SDB, defined as AHI > 5 events/h, was found in nearly 92% of patients, and 34% of patients had severe SDB (AHI > 30 events/h). Age was higher with higher AHI (P = .003). BMI and duration of diabetes were increasingly higher with greater AHI (P = .014 and P = .023, respectively). There was no significant difference among SDB severity groups with regard to sex, wound classification, wound duration (Table 1), and comorbidities (**Table S1** in the supplemental material).

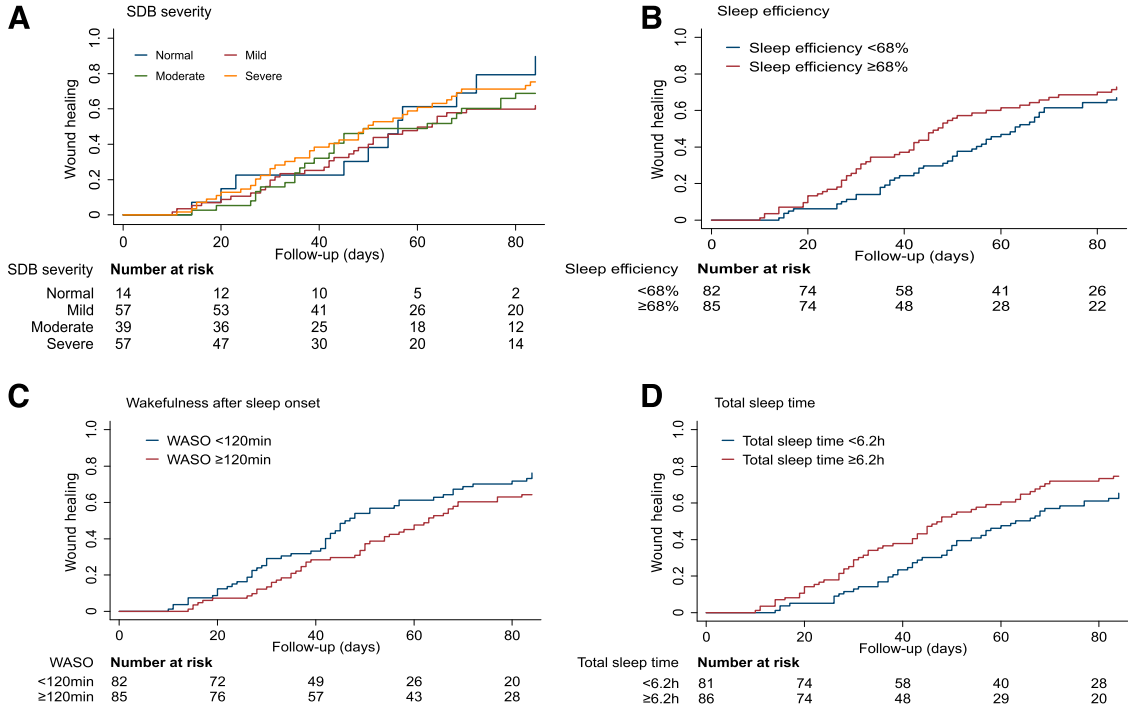
On average, sleep duration was 6.0 ± 1.8 hours and sleep efficiency was 66.0% ± 16.0%. Arousal index, T90%, and oxygen desaturation index increased with higher AHI levels (P < .001, P = .001, and P < .001, respectively) and mean oxygen saturation decreased (P = .002; Table 1). There was no significant difference in sleep measures, such as AHI, total sleep time, sleep efficiency, WASO, T90%, mean oxygen saturation, and oxygen desaturation index among different Wagner grade groups (**Table S2**).

SDB and wound healing

Of the 167 patients, 106 DFUs healed within 12 weeks, yielding an overall healing rate of 63.47%. Kaplan-Meier survival analysis showed that there was no significant difference across SDB severity (log-rank P = .438; Figure 1A). Consistently, the Cox model showed no association between SDB severity and wound healing in crude models and after adjusting for age, sex, BMI, Wagner grade, and wound duration (**Table S3**). In a sensitivity analysis, we modeled AHI as a binary variable testing different thresholds (5 events/h, 15 events/h, 30 events/h) and obtained similar, nonsignificant results (log-rank P = .456, P = .380, and P = .225, respectively; **Figure S1** in the supplemental material). Treating AHI as a continuous variable again yielded no evidence of an association between AHI and wound healing in either univariate (per 5 events/h: HR, 1.02; 95% CI, 0.98–1.07; P = .356) or multivariable models (per 5 events/h: HR. 1.02; 95% CI, 0.97–1.07; P = .411; Table 2).

Kaplan-Meier plots of total sleep time, sleep efficiency, and WASO by median cutoffs are shown in Figure 1B, Figure 1C, and Figure 1D. The median cutoffs of total sleep time, sleep efficiency, and WASO were 6.2 hours, 68%, and 120 minutes, respectively. In unadjusted analysis, total sleep time was associated with wound healing (log-rank P = .047). After

Figure 1—Kaplan-Meier plots of wound healing.



Kaplan-Meier plots of wound healing by SDB severity **(A)**, sleep efficiency **(B)**, WASO **(C)**, and total sleep time **(D)**. SDB = sleep-disordered breathing, WASO = wakefulness after sleep onset.

Table 2—Association of sleep measures with wound healing.

	Unadjusted		Adjusted*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sleep latency (per 10 min)	0.98 (0.91–1.06)	.688	0.97 (0.89–1.06)	.533
Total sleep time (per h)	1.10 (0.99–1.23)	.080	1.15 (1.01–1.30)	.029
Sleep efficiency (per 10%)	1.13 (0.99–1.27)	.050	1.20 (1.04–1.37)	.012
WASO (per 30 min)	0.90 (0.84–0.98)	.010	0.89 (0.82–0.97)	.008
Arousal index (per 5 events/h)	1.02 (1.00–1.05)	.042	1.02 (0.99–1.04)	.052
AHI (per 5 events/h)	1.02 (0.98–1.07)	.356	1.02 (0.97–1.07)	.411
T90% (per 10%)	1.04 (0.96–1.13)	.371	1.04 (0.95–1.14)	.416
Mean oxygen saturation (per 3%)	1.01 (0.85–1.19)	.906	1.01 (0.82–1.23)	.947
Oxygen desaturation index (per 10 events/h)	1.03 (0.93–1.13)	.578	1.04 (0.94–1.15)	.420

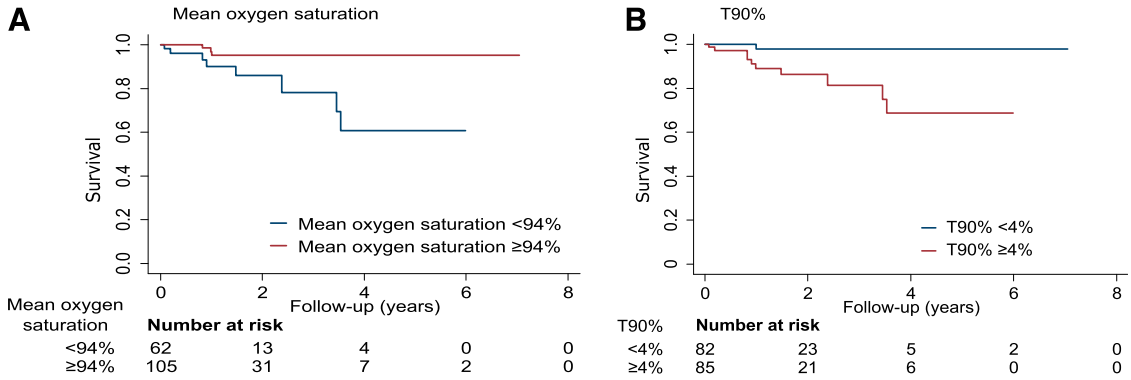
*Adjusted for age, sex, BMI, Wagner grade of ulcers, and wound duration. BMI = body mass index, HR = hazard ratio, T90% = percentage of time with oxygen saturation < 90%, WASO = wakefulness after sleep onset.

correcting for age, sex, BMI, Wagner grade of ulcers, and wound duration, total sleep time (HR, 1.69; 95% CI, 1.10–2.57; P = .015), sleep efficiency (HR, 1.52; 95% CI, 1.00–2.30; P = .047), and WASO (HR, 0.61; 95% CI, 0.41–0.92; P = .017) were found to be significantly associated with wound healing (**Table S4**). When we treated these sleep measures as a continuous variable, higher total sleep time (per hour: HR, 1.15; 95% CI, 1.01–1.30; P = .029) and sleep efficiency (per 10%: HR, 1.20; 95% CI, 1.04–1.37; P = .012) remained associated with a greater likelihood of wound healing in the adjusted analysis. Conversely, a higher WASO (per 30 minutes: HR, 0.89; 95% CI, 0.82–0.97; P = .008) was associated with lower wound healing (**Table 2**). There was no significant relationship of sleep latency, arousal index, oxygen desaturation index, mean oxygen saturation, and T90% with wound healing in the adjusted analysis (**Table 2**).

SDB and amputation

During the 12-week period, 9 patients (5.4%) had to undergo foot amputation. Three amputations were performed on patients with moderate SDB and 6 on patients with severe SDB. Hence, patients with no SDB and those with mild or moderate SDB were pooled together for this analysis. Relative to patients with AHI < 30 events/h, patients with severe SDB had a greater risk of foot

Figure 2—Kaplan-Meier plots of mortality.



Kaplan-Meier plots of mortality in patients with DFUs by mean oxygen saturation **(A)** and T90% **(B)**. DFU = diabetic foot ulcers, T90% = percentage of time with oxygen saturation < 90%.

Table 3—Association of sleep measures and mortality.

	Unadjusted		Adjusted*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Total sleep time (per h)	1.25 (0.84–1.86)	.274	1.21 (0.82–1.77)	.329
Sleep efficiency (per 10%)	1.12 (0.74–1.69)	.604	1.12 (0.74–1.70)	.578
Arousal index (per 5 events/h)	1.01 (0.96–1.05)	.792	1.00 (0.94–1.07)	.929
WASO (per 30 min)	0.89 (0.69-1.16)	.405	0.88 (0.67–1.15)	.349
Oxygen desaturation index (per 10 events/h)	1.14 (0.87–1.50)	.342	1.12 (0.82–1.54)	.470
AHI (per 5 events/h)	1.05 (0.91–1.21)	.505	1.05 (0.89–1.24)	.583
Mean oxygen saturation (per 3%)†	0.55 (0.41–0.74)	< .001	0.68 (0.49–0.94)	.021
T90% (per 10%)	1.25 (1.04–1.51)	.018	1.25 (1.03–1.53)	.026

*Adjusted for age, sex, BMI, and Wagner grade. †For mean oxygen saturation, the HRs for 1% higher of mean oxygen saturation were as follows: unadjusted HR, 0.82 (95% CI, 0.74–0.90) and adjusted HR, 0.88 (95% CI, 0.79–0.98). BMI = body mass index, HR = hazard ratio, T90% = percentage of time with oxygen saturation < 90%, WASO = wakefulness after sleep onset.

amputation (odds ratio, 4.20; 95% CI, 1.01–17.45; $P = .049$) in the unadjusted model. However, this association did not withstand corrections for age, sex, BMI, Wagner grade of the ulcers, and wound duration (odds ratio, 3.17; 95% CI, 0.67–14.97; $P = .145$). Other sleep measures were not significantly associated with amputation (**Table S5**).

SDB and ulcer recurrence

During a median follow-up of 21 months (interquartile range, 15–33 months), 17 patients experienced wound recurrence (14.7%), with 51 patients lost to follow-up. Four patients experienced recurrence more than once. Both higher total sleep time (per hour: odds ratio, 0.71; 95% CI, 0.51–0.97; $P = .035$) and sleep efficiency (per 10%: odds ratio, 0.68; 95% CI, 0.47–0.97; $P = .033$) were associated with lower ulcer recurrence in the multivariable models. No other relationships were found (**Table S6**).

SDB and all-cause mortality

Among the 167 patients, 11 patients (9.5%) died (median follow-up 21 months [interquartile range, 15–33 months]). In the Kaplan-Meier survival analysis, mean oxygen saturation and T90% were significantly associated with all-cause mortality (log-rank $P = .011$ and $P = .010$, respectively; **Figure 2**). After considering age, sex, BMI, and Wagner grade, mean oxygen saturation (HR, 0.20; 95% CI, 0.05–0.79; $P = .021$) and T90% (HR, 9.75; 95% CI, 1.19–79.83; $P = .034$) were significantly associated with all-cause mortality (**Table S7**). In an analysis in which mean oxygen saturation and T90% were modeled as continuous variables, lower mean oxygen saturation (per 3%: HR, 0.68; 95% CI, 0.49–0.94; $P = .021$) and higher T90% (per 10%: HR, 1.25; 95% CI, 1.03–1.53; $P = .026$) were significantly associated with higher mortality in the multivariable models. Oxygen desaturation index, total sleep time, sleep efficiency, and WASO were not significantly associated with death (**Table 3**).

DISCUSSION

In this study of patients with DFUs, the prevalence of SDB was strikingly elevated, with 92% diagnosed with SDB and 34% with severe SDB. Notwithstanding this finding, SDB severity was not associated with DFU outcomes including wound healing, ulcer recurrence, and limb amputation. However, nocturnal hypoxemia predicted death in patients with DFU. Notably, other PSG-derived measures such as total sleep time

and metrics of sleep fragmentation (ie, sleep efficiency and WASO) were significantly associated with wound healing and recurrence.

To date, only few studies have investigated the association of SDB with wound healing, and our study is the first to investigate the impact of SDB on wound healing using prospectively acquired PSG data. In a study of 94 patients with DFUs, Maltese et al[10] found that a STOP-BANG score ≥ 4 predicted poor DFU healing, whereas a study from the Mayo Clinic including 307 patients with amputation site wounds suggested that a prior diagnosis of SDB did not impair healing of partial foot amputation.[11] The use of continuous positive airway pressure treatment may explain the higher wound healing rate observed in patients with SDB in the latter study, although only a small proportion of patients (28%) received treatment. Our study found that AHI was not associated with wound healing within the 12-week follow up. Notably, we consistently observed null findings irrespective of the AHI threshold used to define SDB and when we treated this measure as a continuous variable, thus corroborating the robustness of our results.

In our study, we found that total sleep time and sleep fragmentation were associated with wound healing and ulcer recurrence. Preclinical studies in obese, db/db mice with type 2 diabetes[14] and experimental sleep restriction studies in healthy human volunteers[15] suggested that sleep fragmentation can significantly delay wound healing. Sleep fragmentation can promote inflammation by increasing proinflammatory cytokines, such as interleukin-1 and tumor necrosis factor-α,[14,16] and/or decreasing chemokines such as interleukin-8.[15] Thus, sleep fragmentation may elicit and perpetuate the inflammatory response. In turn, chronic inflammation can lead to impaired angiogenesis, impaired cell migration, and disorganized granulation,[17] hence compromising wound healing in these patients. Furthermore, sleep fragmentation can increase insulin resistance via activation of oxidative stress and inflammatory pathways[18] and induce obesity via leptin resistance.[19] Altered glucose homeostasis may also be implicated by disruption of sleep duration and quality.[20] Therefore, sleep quantity and sleep fragmentation could impact wound healing via multiple mechanisms.

In our study, there was no significant association of AHI with wound healing and mortality, whereas measures of nocturnal hypoxemia (ie, mean oxygen saturation and T90%) were associated with an increased risk of mortality. In clinical practice, the diagnosis and severity grading of SDB are based upon AHI levels. However, accumulating evidence suggests that hypoxic burden, rather than AHI, is a powerful predictor of adverse outcomes in patients with SDB.[21–23] It is increasingly recognized that patients with similar AHIs may have vastly different underlying pathophysiological determinants, symptoms, and polysomnographic expression of SDB (eg, severity of hypoxemia and sleep architecture changes), all of which may affect prognosis, especially in terms of cardiometabolic disease and mortality. Our study corroborates the concept that AHI does not capture the heterogeneity of SDB and thus may not predict SDB-associated outcomes.[24]

Our study has several limitations. First, PSG was performed as an inpatient procedure and the hospital setting may have affected sleep, as suggested by the relatively low sleep efficiency found in our sample. Second, because only 1 night of PSG was conducted, it is also possible that sleep may have been further impacted by the so-called first-night effect, thus potentially reducing data representativeness. Third, we do not have information on whether any patients with SDB received treatment for this sleep disorder after discharge. It is possible that SDB therapy may have influenced outcomes. However, given the very low rate of SDB treatment in the Chinese population, it is unlikely that SDB therapy influenced our results.[25,26] Fourth, in terms of mortality, the relatively high loss-to-follow-up rate (31%) may have biased the evaluation of the impact of SDB on mortality. However, the comparable demographic characteristic and sleep measures between patients included in the analysis and those who were lost to follow-up (**Table S8**) suggest that this finding may not have seriously influenced the results. Fifth, because of the relatively low event rate of amputation and mortality, a larger sample size and longer follow-up may be needed to confirm our findings. Finally, selection bias may not be excluded because patients were recruited from a tertiary center.

The results we report have implications for clinical practice. SDB is a heterogeneous disorder in terms of pathogenesis and clinical manifestation, comprising breathing disturbance, autonomic dysregulation, hypoxemia, and sleep fragmentation.[24] In addition, SDB signs and symptoms are variously associated with cardiovascular risk.[27] As shown by our data, whereas respiratory events during sleep did not predict outcomes, other quantitative measures of disrupted sleep and hypoxemia were strongly associated with wound-related complications. This finding speaks to the need to comprehensively evaluate PSG metrics to improve risk stratification in patients with DFUs and SDB.

Furthermore, asymptomatic patients may not benefit from SDB treatment as much as symptomatic patients. In a randomized trial, patients with severe SDB but no excessive daytime sleepiness in fact did not experience cardiovascular advantages from continuous positive airway pressure therapy, the mainstay treatment for SDB.[28] In addition, the absence of symptoms such as sleepiness may result in poor treatment adherence.[29] On the other hand, supplementary oxygen may be beneficial in patients who experience oxygen desaturation,[30] although whether this treatment improves outcomes remains unclear.

Therefore, given the multiple SDB phenotypes and related patterns of risk and response to treatment,[23,27,28] individualized therapeutic approaches taking these elements into account are warranted. It is relevant to note that because PSG is costly and labor-intensive, other methods that can capture measures of sleep fragmentation and hypoxia may be explored. The widespread availability of smartphones and wearable devices using an array of embedded accelerometers, temperature sensors, and heart rate sensors to estimate sleep characteristics and pulse oxygen saturation represents an attractive alternative.[31] These devices have the added benefit of being minimally obtrusive and allowing multiple nights of recording, thus allowing acquisition of data that would be more representative of routine sleep patterns and could be easily used as screening and risk

stratification tools. However, the validation of these devices needs to be considered.

In conclusion, we found that although SDB was highly prevalent in patients with DFUs, conventional measures of SDB severity such as AHI were not associated with wound-associated outcomes. Conversely, sleep quantity and sleep fragmentation were associated with wound healing and ulcer recurrence and hypoxemia was associated with an increased risk of death in these patients. Given the multifaceted pathophysiology and clinical presentation of SDB, metrics such as sleep quantity, sleep fragmentation, and hypoxemia-based measures may be stronger predictors of SDB outcomes in patients with DFUs than measures of event frequency (ie, AHI). Further research is needed to determine whether our results can be replicated in a larger population and whether targeting these metrics for treatment, for instance by oxygen supplementation in addition to continuous positive airway pressure, could improve wound healing, prevent ulcer recurrence, and reduce mortality.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CI, confidence interval
DFU, diabetic foot ulcer
HR, hazard ratio
PSG, polysomnography
SDB, sleep-disordered breathing
T90%, percentage of time with oxygen saturation < 90%
WASO, wakefulness after sleep onset

REFERENCES

1. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med.* 2017;376(24):2367–2375.
2. Bommer C, Heesemann E, Sagalova V, et al. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. *Lancet Diabetes Endocrinol.* 2017;5(6):423–430.
3. Grote L. The global burden of sleep apnoea. *Lancet Respir Med.* 2019;7(8):645–647.
4. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet.* 2014;383(9918):736–747.
5. Ma W, Chen L, Tang X, Ran X. Obstructive sleep apnea and diabetic foot: a novel research target? *Clin Focus*. 2019;34(8):4:677–680.
6. Subramanian A, Adderley NJ, Tracy A, et al. Risk of incident obstructive sleep apnea among patients with type 2 diabetes. *Diabetes Care*. 2019;42(5):954–963.
7. Khalil M, Power N, Graham E, Deschênes SS, Schmitz N. The association between sleep and diabetes outcomes—a systematic review. *Diabetes Res Clin Pract.* 2020;161:108035.
8. Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic neuropathy: a novel association in patients with type 2 diabetes. *Am J Respir Crit Care Med.* 2012;186(5):434–441.
9. Schaefer CA, Adam L, Weisser-Thomas J, et al. High prevalence of peripheral arterial disease in patients with obstructive sleep apnoea. *Clin Res Cardiol.* 2015;104(9):719–726.
10. Maltese G, Fountoulakis N, Drakatos P, et al. Elevated obstructive sleep apnoea risk score is associated with poor healing of diabetic foot ulcers: a prospective cohort study. *Diabet Med.* 2018;35(11):1494–1498.
11. Andrews KL, Dib M, Shives TC, Hoskin TL, Liedl DA, Boon AJ. The effect of obstructive sleep apnea on amputation site healing. *J Vasc Nurs.* 2012;30(2):61–63.
12. Chinese Diabetes Society, Chinese Society of Infectious Diseases, Chinese Society for Tissue Repair and Regeneration. Chinese guideline on prevention and management of diabetic foot (2019 edition). *Chin J Diabetes Mellitus*. 2019;11(2).
13. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2012;8(5):597–619.
14. McLain JM, Alami WH, Glovak ZT, et al. Sleep fragmentation delays wound healing in a mouse model of type 2 diabetes. *Sleep*. 2018;41(11):zsy156.
15. Smith TJ, Wilson MA, Karl JP, et al. Impact of sleep restriction on local immune response and skin barrier restoration with and without "multinutrient" nutrition intervention. *J Appl Physiol.* 2018;124(1):190–200.
16. Dumaine JE, Ashley NT. Acute sleep fragmentation induces tissue-specific changes in cytokine gene expression and increases serum corticosterone concentration. *Am J Physiol Regul Integr Comp Physiol.* 2015;308(12):R1062–R1069.
17. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol.* 2007;127(3):514–525.
18. Zhang SX, Khalyfa A, Wang Y, et al. Sleep fragmentation promotes NADPH oxidase 2-mediated adipose tissue inflammation leading to insulin resistance in mice. *Int J Obes Lond*. 2014;38(4):619–624.
19. Wang Y, Carreras A, Lee S, et al. Chronic sleep fragmentation promotes obesity in young adult mice. *Obesity (Silver Spring)*. 2014;22(3):758–762.
20. Lee SWH, Ng KY, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Sleep Med Rev.* 2017;31:91–101.
21. Jhamb M, Ran X, Abdalla H, et al. Association of sleep apnea with mortality in patients with advanced kidney disease. *Clin J Am Soc Nephrol.* 2020;15(2):182–190.
22. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J.* 2019;40(14):1149–1157.
23. Zinchuk AV, Jeon S, Koo BB, et al. Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. *Thorax*. 2018;73(5):472–480.
24. Edwards BA, Redline S, Sands SA, Owens RL. More than the sum of the respiratory events: personalized medicine approaches for obstructive sleep apnea. *Am J Respir Crit Care Med.* 2019;200(6):691–703.
25. Liao WJ, Song LJ, Yi HL, et al. Treatment choice by patients with obstructive sleep apnea: data from two centers in China. *J Thorac Dis.* 2018;10(3):1941–1950.
26. Ng SS, Chan TO, To KW, et al. Prevalence of obstructive sleep apnea syndrome and CPAP adherence in the elderly Chinese population. *PLoS One*. 2015;10(3):e0119829.
27. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med.* 2019;200(4):493–506.
28. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA Randomized Controlled Trial. *Am J Respir Crit Care Med.* 2016;194(5):613–620.
29. Luyster FS, Strollo PJ Jr, Thunström E, Peker Y. Long-term use of continuous positive airway pressure therapy in coronary artery disease patients with nonsleepy obstructive sleep apnea. *Clin Cardiol.* 2017;40(12):1297–1302.
30. Turnbull CD, Sen D, Kohler M, Petousi N, Stradling JR. Effect of supplemental oxygen on blood pressure in obstructive sleep apnea (SOX). A randomized continuous positive airway pressure withdrawal trial. *Am J Respir Crit Care Med.* 2019;199(2):211–219.
31. Garde A, Dekhordi P, Ansermino JM, Dumont GA. Identifying individual sleep apnea/hypoapnea epochs using smartphone-based pulse oximetry. *Annu Int Conf IEEE Eng Med Biol Soc.* 2016;2016:3195–3198.

ACKNOWLEDGMENTS

The authors thank Guanjian Liu (West China Hospital, Sichuan University) for his help in the statistical analysis.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September 30, 2020
Submitted in final revised form December 3, 2020
Accepted for publication December 4, 2020
Address correspondence to: Xingwu Ran, Diabetic Foot Care Center, Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, 37 Guo Xue Lane, Chengdu 610041, China; Tel: +86 18980601305;
Email: ranxingwu@163.com and Xiangdong Tang, Sleep Medicine Center, Mental Health Center, Translational Neuroscience Center, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, 28 Dian Xin Nan Jie, Chengdu 610041, China; Tel: +86 18980602059; Email: 2372564613@qq.com

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. This study was funded by the National Science and Technology Major Project (grant number 2017ZX09304023), the Science and Technology Bureau of Chengdu city (grant number 2017-CY02-00028-GX), the Health Medical Big Data Application and Innovation Project in Sichuan (grant number 2018gfgw001), the 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (grant number ZYGD18025), the National Key R&D Program of China (grant number 2017YFC1309605), and the National Natural Science Foundation of China (grant number 81530002). The authors report no conflicts of interest.