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Raised obstructive sleep apnoea risk score is associated with poor healing of diabetic foot ulcers: a prospective cohort study.

Giuseppe Maltese [1], Nikolaos Fountoulakis [1], Panagis Drakatos [2], Dimple Shah [1], Karishma Patel [1], Angelica Sharma[1], Stephen Thomas [1], Martino F Pengo [2], Janaka Karalliedde[1].

[1]Department of Diabetes and Endocrinology, Guy's and St Thomas' NHS Trust, London, UK.

[2]Sleep Disorders Centre, Guy's and St Thomas' NHS Trust, London, UK.

Running title: sleep apnoea risk impairs diabetic foot ulcers healing

*G.M. and N.F. have contributed equally to this work.

Corresponding author: Dr Janaka Karalliedde
150 Stamford Street
London SE1 9NH, UK
Tel: +44 (0) 207 848 4297
Email: j.karalliedde@kcl.ac.uk

Novelty statement

- The impact of risk factors for Obstructive sleep apnoea (OSA) on diabetic foot ulcer healing is unknown.

- We describe for the first time a high prevalence (60%) of risk factors for OSA in patients with diabetic foot ulcers.

- We also report in this prospective study the novel finding that a high risk of OSA predicts, independent of traditional risk factors, a more than a two-fold increased risk of poor diabetic foot ulcer healing.

- Our results support the hypothesis that OSA is a potential modifiable risk factor/treatment target to improve diabetic foot ulcer outcomes.

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Abstract

Background: Obstructive sleep apnoea (OSA) is common in people with diabetes and is associated with oxidative stress, lower nerve fibre density and peripheral neuropathy. The prevalence of risk factors for OSA in people with diabetic foot ulcers is unknown and whether this risk predicts diabetic foot ulcer healing has not been studied.

Material and Methods: We studied 94 (69% men) consecutive people with diabetic foot ulcers (T2DM=66, T1DM=28) attending university hospital foot unit. All participants were screened for OSA by the STOP-BANG questionnaire with a score ≥4 identifying high risk of OSA. Primary outcome was poor diabetic foot ulcer healing defined as diabetic foot ulcer re-occurrence (diabetic foot ulcers which healed and re-ulcerated in same anatomical position) and diabetic foot ulcer persistence (no evidence of healing on clinical examination). All participants were evaluated at 12 months.

Results: Of the 94 participants, 60 (64%) had STOP-BANG score ≥4. Over 12 months, 27 patients with score ≥4 had poor diabetic foot ulcer healing as compared to 7 with a score <4 (45% vs.20.5%) p=0.025. A STOP-BANG score ≥4 significantly increased the relative risk of poor healing by more than two-fold, independent of other risk factors in multivariate analyses.

Conclusions

There is a high prevalence of features and risk for OSA in people with diabetic foot ulcers. A STOP-BANG score ≥4 predicts poor diabetic foot ulcer healing. OSA maybe a potential modifiable risk factor/treatment target to improve diabetic foot ulcer outcomes.

Key words: Diabetic foot, Sleep, microvascular disease

Introduction

Poor healing or non healing diabetes related foot ulcers represents a major complication of diabetes associated with high risk of lower limb amputation and increased mortality (1). In 2010/2011 nearly £1 billion was spent in the UK for diabetes related foot ulcers and resultant amputations and this figure is expected to increase to £2.2 billion by 2035 (2). These statistics denote direct healthcare expenditure, and do not capture indirect costs to the patients, their employers, carers and society. The healing rate of diabetes related foot ulcers in patients treated with standard care is around 50% at 4 weeks; in recent clinical trials only an additional 18-25% of the 'hard to heal' ulcers healed after a further 12 weeks of care (3, 4). New strategies and interventions that improve the healing rates would translate to enhanced patient quality of life, reduced health-related costs and lower limb amputations.

Decreased blood supply with subsequent hypoxia in patients with diabetes often accounts for delayed diabetic foot ulcer healing (4). Obstructive sleep apnoea (OSA) is a breathing disorder characterized by recurrent collapse of the upper tract respiratory airway and intermittent hypoxigenation during sleep causing sleep disruption and excessive daytime sleepiness (5). OSA is a recognised risk factor for cardiovascular disease (CVD) and is associated with increased oxidative stress and inflammation (5) . OSA prevalence in people with diabetes is varied with prevalence rates between 24% to 86 % reported in both type 1 (T1DM) and type 2 diabetes (T2DM) depending on the populations studied and the diagnostic criteria for OSA utilised (5, 6). A recent study reported that the prevalence of OSA in patients with non-diabetic chronic wounds is nearly 10-fold higher than in general population (7). In another cross-sectional study in people with T2DM, 64% were diagnosed with co-existent OSA and the authors observed a more than 3-fold higher prevalence of a history of diabetic foot ulcers in those with OSA (26.2% vs 7.1%) as compared to those without OSA (8). The same group also described increased activation of markers of oxidative stress, pro-inflammatory cytokines and

lower intra-epidermal nerve fibre density in patients with OSA (9). In parallel intermittent hypoxia and subsequent reoxygenation may lead to hypoxia/reperfusion injury with resultant increased oxidative stress and production of vascular growth factors which can further impair wound healing (8, 10).

The Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and male Gender (STOP-BANG) questionnaire is a validated, easy to use, reliable and concise screening tool to identify those at risk of OSA (11, 12).

Diabetes-specific data on the prevalence or clinical impact of risk factors for OSA on acute or chronic diabetes related foot ulcers are lacking. We therefore administered the STOP-Bang questionnaire to identify prevalence of risk for severe OSA in a cohort of people with diabetic foot ulcers and if an abnormal STOP-bang score is associated with unfavorable diabetes related foot ulcer outcomes.

Material and Methods

Participants

We performed a prospective observational cohort study in 94 consecutive persons with diabetes related foot ulcers who had been attending the diabetic foot clinic service for at least 2 months at Guy's and St Thomas' Hospital in London. Participants were recruited between 2014 and 2016. Pre-diagnosed OSA, end-stage renal disease and non-diabetic neuropathy were exclusion criteria. This study was conducted as a part of a service improvement project approved by Guy's and St Thomas' Hospital with informed consent obtained from each participant.

Methods

OSA risk was the exposure and identified using the STOP-BANG questionnaire. The STOP-BANG score ranges from 0-8. Participants were stratified as either at low risk for OSA (score <4 i.e. 0-3) or high risk OSA (score≥4). In a recent meta-analysis validating the use of STOP-BANG in different populations with range of body mass indices (from 26 to nearly 38 kg/m^2)

a score of ≥4 had a sensitivity between 76% to 85% and higher specificity (71-73%) and positive predictive values (52-95%) than lower cut offs for identifying OSA (13).

Peripheral vascular disease (PVD) was confirmed from clinical records and vascular imaging studies. Cardiovascular disease (CVD) was defined as prior history of ischaemic heart disease or cerebrovascular disease from medical records. The Site, Ischemia, Neuropathy, Bacterial Infection, and Depth (SINBAD) score was used to characterise baseline diabetic foot ulcers severity (14). In our study participants who had a score ≥4 were referred to sleep unit for further evaluation.

Primary outcome

The primary outcome was poor healing of diabetic foot ulcer (as a dichotomous variable) which was defined as diabetic foot ulcer persistence and or diabetic foot ulcer re-occurrence at 12 months. Diabetic foot ulcer persistence was defined as a non-healing wound confirmed on clinical examination extending through the dermis. Diabetic foot ulcer re-occurrence was defined as re-ulceration of a previously healed ulcer in the same anatomical position.

Statistical methods

We estimated for this pilot study we would need to study at least 80 participants to detect a risk difference of 30% in poor healing (assuming a 20% prevalence of poor healing in those at low risk of OSA as compared to 50% in those at high risk of OSA) at 80% power, with a two sided significance level of 95%. In total we estimated 92 participants would need to be studied if a 15% drop out rate was observed. As there was no available data to guide a formal sample size calculation we estimated the above effect for our pilot study based on our clinical observations and experience that high OSA risk was associated with nearly 2.5 fold higher rate of poor ulcer healing.

All participants had the primary outcome assessment at 12 months by members of diabetes foot team. Members of the diabetes foot team were blinded to baseline STOP-BANG score.

Data are presented as mean (SD) or median (interquartile range). Independent continuous variables were compared using the Student t test or the Mann-Whitney test. Categorical variables were compared using the Chi squared test.

For assessment of whether abnormal STOP-BANG questionnaire was independently associated with primary outcome multiple logistic regression analysis was performed and relative risk and 95% confidence intervals (95% CI) are reported (15). To build the logistic regression model we used a hierarchical block entry method of entering predictor variables. Variables included in the model were based on variables that were significantly different between high and low risk OSA groups. Based on the assumption that we would need at least 10 cases per independent variable to avoid overfitting we allowed for up to four independent variables to be included in the model. Forced entry , backward and forward stepwise procedures were also used to verify the variables that determined the best prediction model.

Raised body mass index (BMI) and risk of OSA are strongly biologically and statistically correlated. As the STOP-BANG score includes a BMI >35kg/m2 as a risk factor to evaluate the impact of the score with less confounding due to raised BMI, we also included as a covariate category of BMI (above or below >35kg/m2) in multivariate analyses. Improvement in model fit with addition of each predictor was assessed by calculating significance of the change of the likelihood ratio. Proportion of variation explained by the model was assessed by Nagelkerke's R^2. Models were tested for multicollinearity, independence of errors and linearity.

Linearity assumption was tested by looking at whether the interaction term between the predictor and its log-transformation is significantly associated with the logit of the outcome variable. Multicollinearity was tested by calculating the variance inflation factor (VIF) with values over 10 indicating a problem. Independence of errors assumption was tested by calculating the dispersion parameter. A value greater than one indicates overdispersion. Thus violating the assumption of independence. To look for cases that might be influencing the

model we looked at standardized residuals as well as influence statistics such as Cook's distance DFbeta and leverage statistics. We assumed that 5% of the standardised residuals should lie outside ±1.96 and about 1% should lie outside ±2.58 so as to isolate points for which the model fits poorly. We also assumed that Cook's distance, DFBeta for predictors should be more than one in order to isolate points that exert an undue influence on the model. Statistical analysis was performed using SPSS 21.0 software (SPSS, Chicago, IL).

Results

A total of 94 (69% male) people consented for this study. Of the cohort 66 (70%) had T2DM, and 28 (30%) T1DM. The median age (range) was 58 (25-87) years with a median duration of diabetes of 16 (2-48) years. Median BMI (interquartile range) of cohort was 28.4 (25 to 32) kg/m^2. Of the 94 patients, 60 (64%) had symptoms suggestive of high risk of OSA with a STOP-BANG questionnaire score $\geq$ 4. There were no dropouts during the study and all participants attended for their final visit at 12 months.

The number (%) participants with a STOP-BANG of 1, 2, 3, 4, 5, 6 and 7 were 9 (9.6%), 11(11.6%), 14 (15%), 29 (31%), 18 (19%), 11 (11.7%) and 2 (2%) respectively. There were no participants with a score of 0 or 8.

Participants were divided into two groups based on a STOP-BANG score <4 or $\geq$ 4 indicative of low or high risk of OSA respectively (Table 1). At baseline, participants with increased risk of OSA (STOP-BANG score $\geq$ 4) had higher age, BMI, blood pressure, greater prevalence PVD, CVD, and lower renal function (Table 1). There was similar prevalence of active infection of ulcers in both groups. SINBAD score or proportion of diabetic foot ulcers >1cm in size were not statistically different between the two groups (Table 1).

A total of 34 participants reached the primary outcome of poor diabetic foot ulcer healing. Participants with STOP-BANG score $\geq$4 had a more than 2-fold higher rate of poor diabetic

foot ulcer healing when compared to those <4 (45% vs.20.5%) p=0.025. Components of the primary outcome were persistent ulcers n=19 (2 in group with score STOP-BANG <4 vs. 17 in those STOP-BANG ≥ 4, p=0.014) and similarly for reoccurrence [n=15 (4 vs. 11 p=0.56)].

In multivariate logistic regression participants with a STOP-BANG score ≥ 4 had more than a two fold higher risk of poor foot ulcer healing as compared to those with score <4 (Table 2). We evaluated the robustness of the models in Table 2 as outlined in statistical methods section. The model which including age and raised STOP-BANG score (model $\chi2=14.177$,p=0.001,Nagelkerke $R^2=0.196$) had the best goodness of fit and model with age, gender , type of diabetes and raised STOP-BANG score had best R^2 of 0.270. A forced entry model gave similar results to model 4 in Table 2. No further improvement was observed with addition of multiple other risk factors. In all the models (forward or backward or enter procedures) a raised STOP-BANG score increased the relative risk of poor ulcer healing by more than two fold independent of multiple traditional risk factors including age, gender, type of diabetes, BMI category, blood pressure, PVD and CVD.

Discussion

This is the first study describing a high prevalence of OSA risk factors among people with diabetic foot ulcers. In our cohort, 64% of participants had a high risk of OSA. We also report for the first time the association between risk of OSA as defined by an increased STOP-BANG score and poor diabetic foot ulcer healing.

There is a reported 24% to 86% prevalence of OSA in T2DM patients and clinical care guidelines propose systematic OSA screening (16). The STOP-BANG questionnaire is a validated and reliable tool for identifying OSA with high specificity and sensitivity (11).

It is well documented that non-treated OSA leads to significant morbidity and worsening glycaemic control as well as to the development of diabetic microvascular complications (17). In patients with diabetes and OSA, intermittent hypoxia increases sympathetic activation and

hereby oxidative stress, impaired microvascular function and inflammation which could all contribute to poorer diabetic foot ulcer outcomes (8). In a cross-sectional study, involving T2DM patients, OSA was associated with diabetic foot ulcers and this association was independent of risk factors such as peripheral artery disease, BMI, age, diabetes duration and HbA1c (9). In a recent case series of three diabetic foot ulcers patients, the authors hypothesized that undiagnosed or untreated severe OSA contributed to failure of diabetic foot ulcer healing and reported that initiation of OSA treatment improved ulcer healing (18). In patients with diabetes and OSA, continuous positive airway pressure (CPAP) treatment appears to have mixed effects on glycaemic control and there is currently limited data on long term progression of diabetes-related eye and renal complications (19-21). Whether CPAP can improve the healing of diabetic foot ulcers requires randomised controlled interventional studies.

Our study is the first prospective study to analyse the impact of risk factors for OSA on the progression of diabetic foot ulcers. We studied a well characterized cohort of T1DM and T2DM patients with diabetic neuropathy attending a single tertiary care unit undergoing treatment for their diabetic foot ulcers with standardised treatment protocols. Our work has several limitations: a) the study design does not allow us to evaluate a dose response relationship; b) the sample size is small as we recruited from only one centre; c) the diagnosis of OSA was not confirmed in individuals at risk by using the gold standard methods; d) the OSA risk cut-off score we utlised needs to be further validated in patients with diabetic foot disease as most studies to data have been in patients from sleep clinics or other clinical settings; e) our study was not designed to evaluate and explore the differential impact of OSA risk on DFU persistence or DFU recurrence which can have distinct aetiologies and pathophysiology and our study design also does not enable us to differentiate if OSA or neuropathy (which share

common risk factors) is driving the outcome or exclude the potential confounding effect of differences in foot ulcer care and duration before participants entered the study.

Studies utilizing gold standard diagnostic tests for OSA, and CPAP treatment are required to give credence to our findings and explore causality between non-healing of diabetic foot ulcers and OSA. Our results establish the proof of principle and clinical rationale for such studies.

In summary, the use of the STOP-Bang questionnaire in a cohort of people with diabetic foot ulcers unveiled a high prevalence of risk factors for OSA, and suggested that a score ≥4 is independently associated with poor diabetic foot ulcer healing. Infection, Ischaemia and inadequate pressure offloading are the 3 classical risk factors for non-healing and our results suggest that OSA is potentially another modifiable risk factor to improve healing. Future interventional studies should examine the impact of OSA treatment on the development and progression of diabetic foot ulcers.

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Table 1. Baseline demographic, clinical and laboratory characteristics of 94 patients with diabetic foot ulcer with STOP-BANG score <4 (low risk of obstructive sleep apnoea) or ≥ 4 (high risk of obstructive sleep apnoea).

Variable	STOP-BANG score <4 (n=34)	STOP-BANG score ≥4 (n=60)	p-value
Age (years)	51.5±16.2	62.7±12.0	0.01
Gender (male %)	15 (44%)	50 (83%)	0.0001
T1DM (%)	21	7	0.0001
T2DM (%)	13	53	
Diabetes duration (years)	19.5 ±12.5	16.9±10.0	0.31
Peripheral vascular disease n (%)	7 (20.6%)	29 (48%)	0.009
Cardiovascular disease	4 (12%)	24 (40%)	0.005
Insulin treatment (%)	27 (82%)	44 (73%)	0.301
Evidence of active infection	7 (21%)	13 (22%)	0.9
SINBAD score*	1 (0 to 1)	1 (0 to 2)	0.27
Diabetic foot ulcers size >1cm	5 (30%)	13 (22%)	0.42
eGFR (ml/min)	94.8±47.4	68.4±37.5	0.004
SBP (mmHg)	135.8±20.7	136.3±18.0	0.90
DBP (mmHg)	77.8±13.3	76.4 ±7.9	0.62
BMI (kg/m^2)	25.3±4.2	30.9±5.4	0.0001
HbA1c (%) (mmol/mol)	8.6±2.2 70±6	8.3±1.8 67±6	0.48

Abbreviations: SBP=systolic blood pressure, DBP=diastolic blood pressure, AER=albumin excretion rate, BMI=body mass index, eGFR=estimated glomerular filtration rate. SINBAD= Site, Ischemia, Neuropathy, Bacterial Infection, and Depth, diabetic foot ulcers = diabetic foot ulcer, STOP-BANG= snoring, tiredness, observed apnea, high blood pressure, body mass index, age, neck circumference, and male gender questionnaire. * median interquartile range

Table 2. Unadjusted and adjusted (for other risk factors) multivariate regression analysis models that demonstrate the relationship between STOP-BANG score ≥4 (high risk of obstructive sleep apnoea) and increased risk of poor diabetic foot ulcer healing

	Relative Risk	95% CI	p-value
Model 1 Unadjusted model STOP-BANG score ≥ 4 only	2.20	1.15 to 3.34	0.021
Model 2 STOP-BANG score ≥ 4 and age	2.17	1.68 to 4.19	0.002
Model 3 STOP-BANG score ≥ 4, age and gender	2.83	1.37 to 4.05	0.009
Model 4 STOP-BANG score ≥ 4, age gender, type of diabetes	2.67	1.14 to 4.03	0.027

Abbreviations:

STOP-BANG= snoring, tiredness, observed apnea, high blood pressure, body mass index (BMI), age, neck circumference, and male gender questionnaire.

Other variables tested were gender, type of diabetes, estimated glomerular filtration rate, cardiovascular disease, peripheral vascular disease and BMI category. There was no additional improvement in model fit but a more than two-fold increased relative risk between raised STOP-BANG score and poor diabetes related foot ulcer healing was observed in all models (all $p<0.05$).