The Impact of Hypoxemia on Nephropathy in Extremely Obese Patients with Type 2 Diabetes Mellitus

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Study Objectives: Diabetes mellitus (DM) is associated with obstructive sleep apnea (OSA) and nephropathy. The hypoxemia associated with OSA may exacerbate renal deterioration in DM nephropathy. We examined the role of hypoxemia in the development of DM nephropathy in severely obese patients.

Methods: This cross-sectional study examined anonymized data from 90 DM patients with extreme obesity attending a weight management service. All patients underwent a routine overnight sleep study. Respiratory parameters measured included apnea-hypopnea index (AHI), mean and minimum oxygen (O₂) saturations, and time spent under 90% O₂ saturation (%TST < 90%). Chronic kidney disease (CKD+) was defined as estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m².

Results: Twenty (22%) patients were CKD+. These patients were 7 years older (mean age ± SD 57 ± 11 years, *p* = 0.003) and had greater adiposity (mean body mass index [BMI] ± SD 50.6 ± 8.7 kg/m², *p* = 0.012). No significant differences were found for median AHI and minimum O₂ saturation. %TST < 90%

was 4 times greater in CKD+ group (*p* = 0.046). Multivariate regression analysis showed that AHI (β = -0.17, 95% CI: -0.316 to -0.024) and %TST < 90% (β = -0.215, 95% CI: -0.406 to -0.023) were negatively correlated with eGFR after adjustment for age, gender, BMI, comorbidities, insulin treatment, and drugs affecting the renin-angiotensin system. No associations were found between mean and minimum O₂ saturations, and eGFR.

Conclusion: Apnea and hypopnea events as well as duration of nocturnal hypoxemia were inversely associated with renal function after adjusting for potential confounders. Given the significant burden of renal disease in diabetes, greater vigilance is required in identifying OSA in DM patients with extreme obesity.

Keywords: sleep disordered breathing, obstructive sleep apnea, diabetes mellitus, diabetes nephropathy, extreme obesity

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The increasing worldwide prevalence of obesity has led to a parallel rise in type 2 diabetes mellitus (DM). DM is associated with macro and micro-vascular complications with significant impact on morbidity and mortality. A common micro-vascular DM complication is diabetic nephropathy. Indeed, DM is a major risk factor for the development of chronic kidney disease (CKD) and subsequent end stage renal disease (ESRD) needing renal replacement treatment (RRT).¹ The UK Prospective Diabetes Study (UKPDS) found that in patients with DM, over 10 years, the incidence of micro-albuminuria was 24.9%, macro-albuminuria prevalence was 5.3%, and the incidence of those with creatinine above 175 micromol/L or needing RRT was 0.8%.²

An increasingly recognized condition associated with DM is obstructive sleep apnea (OSA).³ OSA is a condition associated with repetitive episodic complete or partial upper airway collapse leading to hypoxemia and activation of sympathetic nervous system activity with downstream effects on blood

BRIEF SUMMARY

Current Knowledge/Study Rationale: Nephropathy is a well-known microvascular complication of diabetes mellitus (DM), and one of the most common causes of chronic kidney disease and end-stage renal disease needing renal replacement therapy. Since DM is also closely associated with obstructive sleep apnea (OSA), our study examined the potential relationship between chronic nocturnal hypoxemia and renal function in DM individuals with extreme obesity.

Study Impact: Our findings demonstrate that not only do apnea and hypopnea episodes have a negative impact on renal function in DM, but also that the duration of nocturnal hypoxemia is important. Our findings suggest that apart from glycemic, blood pressure, and lipid control, there is potentially also a need to consider treatment of hypoxemia in efforts to preserve and delay progression of renal disease among DM individuals.

pressure and vascular disease. Few studies have examined the impact of concurrent OSA on DM microvascular complications. Nocturnal hypoxemia has been reported to be potentially associated with diabetic retinal disease⁴ as well as diabetic neuropathy.⁵

Currently, there is no information on the impact of OSA on renal function in DM individuals with extreme obesity (body mass index [BMI] of at least 40 kg/m²), an increasingly important clinical population. We examined the prevalence of OSA amongst extreme obese DM patients. We also explored the characteristics of DM patients with CKD stage 3 and below to investigate the role of OSA (nocturnal hypoxemia) in kidney disease.

METHODS

Anonymized data from prospective DM patients who attended the regional specialist weight management service at the Heart of England NHS Foundation Trust between 2009 and 2011 were included. As obesity is a well-recognized risk factor for OSA, all patients had an overnight sleep study performed as part of a comprehensive routine clinical assessment. Routine demographic, physical examination, DM history and comorbidity data were collected. Demographic and physical examination data included age, gender, self-reported ethnicity, and objective measures of weight, height, and BMI. Comorbidity history included hypertension and coronary artery disease (CAD). The duration of DM, anti-diabetes medication, and HbA_{1c} (DCCT-aligned and IFCC) and serum creatinine were also obtained. Data on treatment with either angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) were also collected. All data were anonymized prior to data analysis.

The estimated glomerular filtration rate (eGFR) was calculated based on recommendations from both the National Institute for Health and Clinical Excellence (NICE)⁶ and the National Kidney Foundation Kidney Disease outcome Quality Initiative Clinical Practice Guidelines⁷ using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation. In addition, we also used the CKD Epidemiology Collaboration (CKD-EPI) equation for regression analysis, as it may provide better accuracy compared to MDRD formula.⁸

Staging of CKD was based on the value of eGFR. Patients with eGFR > 90 mL/min/1.73 m² had CKD stage 1; eGFR of between 60 and 90 mL/min/1.73 m² was classified as stage 2; eGFR 30 to 60 mL/min/1.73 m² was stage 3; eGFR 15 to 30 mL/min/1.73 m² was stage 4; and eGFR < 15 mL/min/1.73 m² was stage 5. Patients with eGFR of < 60 mL/min/1.73 m² were grouped as CKD+, while those with eGFR > 60 mL/min/1.73 m² were categorized as CKD– using the MDRD calculation.

The sleep clinical service protocol used the home portable Embletta (Embla systems) for overnight sleep studies. Demonstrations and instructions were given to patients by trained sleep physiologists on the day of examination. Patients were observed applying the device by staff during the demonstration session and the device was returned to the unit the next day. The device included a nasal cannula to measure airflow, inductance plethysmography for thoracic and abdominal movements, and pulse oximetry to measure oxygen saturations and heart rate. It also measured body position. At least 4 h of good quality respiratory signals were deemed appropriate for scoring. A retest for the sleep study was offered if inadequate readings were present.

Blinded sleep physiologists manually scored all respiratory data. Subsequently, author DB re-scored and confirmed all

results. Both sleep physiologists and author DB were blinded to the renal results. The respiratory scoring was done based on the American Academy of Sleep Medicine recommended sleep scoring guidelines.⁹ Respiratory parameters collected included the apnea-hypopnea index (AHI), the percentage of time spent under 90% oxygen saturation (%TST < 90%), and mean and minimum oxygen saturation during sleep. An apnea was defined as no airflow for ≥ 10 sec, while an obstructive hypopnea was defined as ≥ 30% reduction in airflow accompanied by ≥ 4% drop in oxygen saturation with the presence of effort from the thorax and abdomen.

Statistical Analyses

Statistical analyses were carried out using Stata 13 (Stata-Corp LP, College Station, Texas). No formal ethical approval was required for this study as it was conducted as part of the weight management and respiratory service evaluation on anonymized data. This is based on the recommendation by the UK National Research Ethics Service.¹⁰ Distribution of data was determined using visual inspection and Shapiro-Wilk test. When eGFR was calculated using CKD-EPI formula, the data were skewed; therefore, log transformation was performed prior to regression analysis. Mean and standard deviation (SD) were used to report parametric data, while median and interquartile ranges (IQR) were used for nonparametric data. Patients were categorized into eGFR of > 60 (CKD– group) and < 60 mL/min/1.73 m² (CKD+ group). Independent *t*-test, Mann-Whitney U test, and χ^2 test were used for analysis of normal distributed data, skewed, and categorical data, respectively. Analyses on associations between eGFR and the respiratory parameters (AHI, %TST < 90%, minimum and mean oxygen saturations) were carried out based on Pearson correlation. Subsequently, linear regression analysis was used for further analysis. Univariate analyses were performed for all the respiratory parameters and eGFR. Model 1 was adjusted for age, gender, and BMI; and Model 2 was adjusted for age, gender, BMI, hypertension, CAD, duration of DM, insulin treatment, and treatment on ACE inhibitor or ARB. The results for linear regression analyses using MDRD eGFR equation were reported as beta coefficient with 95% confidence interval (95% CI). Regression results for log transformed eGFR based on CKD-EPI formula were back transformed and were reported as percentage change with 95% CI. A *p* value < 0.05 was considered significant.

RESULTS

A total of 116 consecutive obese DM patients were seen at the service between 2009 and 2011. However, one patient's anthropometry data were not available, 9 did not have renal function tests performed, and 16 patients' respiratory parameters were not complete for analysis. This resulted in data from 90 eligible patients for analysis. None of the patients had a diagnosis of central sleep apnea.

The mean age was 51 ± 10 years with slightly more females (57%) and the majority were white Europeans (91%). The mean BMI was 46.8 ± 7.7 kg/m², with 61% of patients having concomitant hypertension and 10% diagnosed with CAD. Median duration of DM was 6 years (IQR 2, 10), with HbA_{1c} of 64 (IQR 51, 80) mmol/mol or 8.0% (IQR 6.8%, 9.5%). The majority of the

Table 1—Sample characteristics of patients with and without at least chronic kidney disease stage 3 (CKD 3) based on MDRD formula

	N	CKD+ (N = 20)	N	CKD- (N = 70)	p value
Age (years)	20	57 ± 11	70	50 ± 9	0.003
Female	16	80%	35	50%	0.017
Ethnicity					0.207
White Europeans	17	85%	47	67%	
South Asians	3	15%	16	23%	
Afro-Caribbean	0	0%	7	10%	
BMI (kg/m ²)	20	50.6 ± 8.7	70	45.7 ± 7.1	0.012
Systolic BP (mm Hg)	17	152 ± 26	50	140 ± 17	0.037
Diastolic BP (mm Hg)	17	88 ± 17	50	83 ± 8	0.095
Comorbidities					
Hypertension	15	75%	40	57%	0.149
Coronary artery disease	5	25%	5	7%	0.025
ACE-I or ARB	15	75.0%	32	57.5%	0.021
ACE inhibitor	6	30.0%	23	18.6%	0.809
ARB	9	45.0%	13	18.6%	0.015
DM Parameters					
DM Duration	20	9 (4, 13)	67	6 (2, 10)	0.149
HbA _{1c} (%)	19	7.5 (6.8, 9)	69	8.1 (6.9, 9.7)	0.503
HbA _{1c} (mmol/mol)	19	58 (51, 75)	69	65 (52, 83)	0.503
Insulin	11	55%	17	24%	0.009
Number of DM Medications					0.814
None	3	15%	15	21%	
1	5	25%	19	34%	
2	10	50%	27	39%	
> 3	2	10%	9	13%	
Respiratory Parameters					
OSA (AHI ≥ 5)	17	85%	58	83%	0.821
AHI ≥ 15	10	50%	36	51%	0.910
AHI (events/h)	20	17 (7, 63)	70	15 (7, 31)	0.600
Mean O ₂ sat (%)	20	92 (91, 94)	70	93 (92, 95)	0.043
Minimum O ₂ sat (%)	20	81 (73, 84)	70	83 (74, 85)	0.268
Time under 90% sat (%)	19	8.6 (1.1, 33.3)	64	2.5 (0.5, 12.1)	0.046

Data are presented as mean ± standard deviation, percentage or median (interquartile range). CKD+, presence of chronic kidney disease stage 3 and below; CKD-, absence of chronic kidney disease stage 3 and below; BMI, body mass index; BP, blood pressure; DM, type 2 diabetes mellitus; AHI, apnea-hypopnea index; O₂, oxygen; sat, saturation. p values were calculated using independent *t*-test, Mann-Whitney U, test or χ^2 test.

patients required ≥ 2 anti-diabetes medications (53%), and 31% were on insulin treatment. The patients had a mean MDRD and CKD-EPI eGFR of 78.3 ± 25.1 and 89.9 ± 21.6 mL/min/1.73 m², respectively. The median AHI was 15 (IQR 7, 37) events/h, mean oxygen saturations of 93% (IQR 92%, 95%), minimum oxygen saturations 82% (IQR 74%, 85%), and %TST < 90% of 2.9% (IQR 0.7%, 15.0%). The prevalence of OSA based on AHI ≥ 5 events/h was 83% (95% CI: 74% to 90%), and the proportion with moderate-to-severe OSA (AHI ≥ 15/h) was 51% (95% CI: 41% to 61%). Of those with a diagnosis of OSA, 22.7% and 13.3% had MDRD and CKD-EPI eGFR of 60 mL/min/1.73 m² and below, respectively.

Twenty-nine per cent of DM individuals did not suffer with CKD (MDRD GFR > 90 mL/min/1.73 m²), while 49% had CKD stage 2. A total of 20 patients had MDRD eGFR < 60 mL/min/1.73 m² (22%, 95% CI: 15% to 32%). None of the patients had CKD stage 5, and only 1 had stage 4 CKD. Using the CKD-EPI equation, a lower proportion (28.9%) had CKD stage

2, 10% had stage 3 (n = 9), while 1 patient had stage 4, and none had stage 5 CKD. Those patients in the MDRD CKD+ group were older with a mean age of 57 ± 11 years compared to those in the MDRD CKD- group (50 ± 9 years, *p* = 0.003) as shown in **Table 1**. No significant differences were found in ethnicity between the groups (*p* = 0.207). There were also significantly more females (80%) in MDRD CKD+ group compared to MDRD CKD- (50%, *p* = 0.017) and greater adiposity in MDRD CKD+ group with BMI of 50.6 ± 8.7 kg/m² compared to 45.7 ± 7.1 kg/m² in MDRD CKD- group (*p* = 0.012). Systolic BP was significantly higher in MDRD CKD+ group (*p* = 0.037), but this was not the case for diastolic BP. Although no difference was found in the proportion with hypertension between the 2 groups, there was at least a 3-fold higher CAD in the MDRD CKD+ group (25% vs. 7%, *p* = 0.025).

There were no significant differences in DM duration and HbA_{1c} levels between the two groups. Insulin usage was at least 2-fold higher in MDRD CKD+ group (*p* = 0.009). A greater

Table 2—Linear regression analysis assessing associations between MDRD eGFR and respiratory parameters

	Reported as Beta Coefficients (95% Confidence Intervals)		
	Univariate models	Model 1	Model 2
AHI	−0.058 (−0.247 to 0.130)	−0.207 (−0.353 to −0.061) *	−0.170 (−0.316 to −0.024) *
Min O ₂ sat	−0.011 (−0.539 to 0.516)	0.202 (−0.241 to 0.645)	0.053 (−0.388 to 0.495)
Mean O ₂	1.413 (−0.0638 to 2.890)	1.494 (0.247 to 2.741) *	1.191 (−0.039 to 2.420)
%TST < 90%	−0.272 (−0.512 to −0.032) *	−0.254 (−0.453 to −0.055) *	−0.215 (−0.406 to −0.023) *

Univariate models: unadjusted. Model 1: adjusted for age, gender, body mass index. Model 2: further adjusted for hypertension, coronary artery disease and duration of type 2 diabetes mellitus, insulin treatment, and angiotensin converting enzyme inhibitor or angiotensin receptor blocker treatment. *p value < 0.05. eGFR, estimated glomerular filtration rate; AHI, apnea-hypopnea index; Min O₂ sat, minimum oxygen saturation; Mean O₂, mean oxygen saturation; %TST < 90%, time spent under 90% oxygen saturation.

Table 3—Linear regression analysis assessing associations between CKD-EPI eGFR and respiratory parameters

	Reported as Percentage Change (95% Confidence Intervals)		
	Univariate models	Model 1	Model 2
AHI	−0.30 (−0.52 to −0.08) *	−0.27 (−0.47 to −0.67) *	−0.19 (−0.39 to 0.01)
Min O ₂ sat	0.74 (0.13 to 1.36) *	0.44 (−0.16 to 1.05)	0.16 (−0.44 to 0.76)
Mean O ₂	3.15 (15.26 to 4.90) *	2.10 (0.38 to 3.86) *	1.50 (−0.21 to 3.22)
%TST < 90%	−0.52 (−0.79 to −0.25) *	−0.38 (−0.65 to −0.11) *	−0.30 (−0.56 to −0.03) *

Univariate models: unadjusted. Model 1: adjusted for age, gender, body mass index. Model 2: further adjusted for hypertension, coronary artery disease and duration of type 2 diabetes mellitus, insulin treatment and angiotensin converting enzyme inhibitor or angiotensin receptor blocker treatment. *p value < 0.05. eGFR, estimated glomerular filtration rate; AHI, apnea-hypopnea index; Min O₂ sat, minimum oxygen saturation; Mean O₂, mean oxygen saturation; %TST < 90%, time spent under 90% oxygen saturation.

proportion of patients were treated with either ACE inhibitor or ARB in MDRD CKD+ group ($p = 0.021$). No significant differences were found in OSA prevalence based on AHI ≥ 5 events/h or in the proportion of moderate-to-severe OSA. AHI and minimum oxygen saturation levels were also not significantly different between the groups. However, there was a significant difference in the mean oxygen saturation ($p = 0.043$), and %TST < 90% was ≥ 3 times higher in MDRD CKD+ patients ($p = 0.046$).

Pearson correlation analysis found no significant correlations between AHI, mean and minimum oxygen saturations, and MDRD eGFR. However, there was a significant correlation between MDRD eGFR and %TST < 90% ($r = -0.24$). This was confirmed with univariate linear regression analysis, with a 0.27% reduction in MDRD eGFR for every 1% increase in %TST < 90% (95% CI: −0.51 to −0.03). No significant results were found for AHI or minimum and mean oxygen saturations with MDRD eGFR as shown in **Table 2**. However, using the CKD-EPI calculation for eGFR, all 4 respiratory parameters were significantly associated with CKD-EPI eGFR as shown in **Table 3**. In Model 1 of the multivariate linear regression analysis using MDRD eGFR, %TST < 90% remained significant ($\beta = -0.25$, 95% CI: −0.45 to −0.06) after adjusting for age, gender, and BMI. AHI ($\beta = -0.21$, 95% CI: −0.35 to −0.05) and mean oxygen saturation ($\beta = 1.49$, 95% CI: 0.25 to 2.74) were also significant in Model 1 based on MDRD formula. No significant association was found for minimum oxygen saturations and MDRD eGFR. CKD-EPI eGFR regression models revealed similar results as MDRD eGFR (**Table 3**).

In Model 2, the associations remained significant after further adjustments for hypertension, CAD, DM duration, insulin treatment, and treatment with ACE inhibitor or ARB. For AHI, there

was a 0.17% reduction in MDRD eGFR (95% CI: −0.32 to −0.02) for each increase in event/h and a 0.22% reduction in MDRD eGFR for each increase in % of %TST < 90% (95% CI: −0.41 to −0.02). Similarly, there were no significant differences found for minimum oxygen saturations with MDRD eGFR. The mean oxygen saturation was not associated with MDRD eGFR after adjustment for the additional variables. Regression models based on CKD-EPI calculation revealed that only %TST < 90 ($\beta = -0.30$, 95% CI: −0.56 to −0.03) was significantly associated with reduction of renal function, as shown in **Table 3**. Model 3 also showed that AHI was approaching statistical significance based on CKD-EPI calculation.

DISCUSSION

Our study found that almost a quarter of extremely obese DM individuals with OSA had CKD stage 3 and below based on MDRD formula, while a lower proportion had stage 3 disease based on CKD-EPI calculation. A recent multi-center Japanese study of hospital-based patients reported that 44.2% of DM with nocturnal hypoxemia suffered with either micro or macro-albuminuria.¹¹ The higher reported rate from the Japanese study may be partly because the researchers examined urine ACR rather than eGFR.¹¹ Another multi-center primary care study found that 15.8% of DM patients who had OSA suffered with nephropathy.¹² The difference in the reported rate may be partly due to older patients as well as a much lower adiposity level than in our study.

The association between chronic nocturnal hypoxemia and renal function has been examined by several studies, with contradictory results.¹¹⁻¹⁷ In DM patients, a study of 52 individuals found no correlation between ACR and respiratory

parameters including AHI.¹³ Another observational study in DM patients found that those with nocturnal intermittent hypoxemia had up to a threefold increase in the odds for macroalbuminuria and up to twofold increased odds for micro-albuminuria.¹¹ Significant differences in DM nephropathy between OSA and non-OSA DM patients were also reported by another group in Germany.¹² We did not find any significant differences in the AHI or prevalence and classification of OSA between CKD+ and CKD- individuals. However, after adjusting for potential confounders, AHI was inversely associated with eGFR, based on the MDRD calculation. Although AHI is not a measurement of intermittent hypoxemia, the repetitive long-term apneic and hypopneic episodes are significantly correlated to oxygen desaturation. Therefore, the effect of AHI may be mediated through episodic intermittent hypoxemia having a negative impact on glomerular function.

Apart from AHI, we also found that the %TST < 90% has an inverse impact on renal function of DM patients, using both the MDRD and CKD-EPI formulas. Only a few studies have explored the relationship between %TST < 90% and renal function.^{13,15,17} A recent study of 858 participants reported that %TST < 90% of > 12% increases the odds for accelerated renal decline threefold.¹⁷ Unruh and colleagues compared 46 dialysis patients matched with 137 individuals with normal renal function from the Sleep Heart Health Study and found that renal patients are four times more likely to have nocturnal hypoxemia than matched individuals.¹⁵ However, these two studies included both DM and non-DM participants. Also, the study by Unruh and colleagues did not perform further adjustment for potential confounders. A recent study of 52 individuals with DM did not find any correlation between urinary ACR and %TST < 90%; this negative result may be due to the small sample size.¹³

Our results show that apart from apneic and hypopneic episodes, the duration of nocturnal hypoxemia also has a potential effect on the kidneys. Several factors may explain the association between AHI as well as %TST < 90% and eGFR. It has been shown in animal models that prolonged exposure to intermittent hypoxemia results in the activation of the renin-angiotensin receptor system as well as increased endothelin-1 levels, which are associated with vasoconstriction and blood pressure elevation.^{18,19} We attempted to correct for the BP and RAS effect by adjusting for hypertension as well as treatment for ACE inhibitor and ARB. The results for the association between AHI and %TST < 90% with eGFR remained significant. This suggests the possibility of other mediators being involved such as inflammation, and oxidative stress and damage.

Both OSA and diabetic nephropathy have been shown to be associated with increased inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α).²⁰⁻²³ These markers have been shown to be associated with cardiovascular disease²⁴ and may also affect renal vasculature. Apart from inflammatory markers, studies have also shown greater oxidative stress markers in both OSA and DM nephropathy.^{25,26} Humoral factors such as leptin may also contribute to the deterioration of renal function. It has been found that patients with diabetic nephropathy have higher level of leptin.²⁷ Similarly, OSA is also associated with greater levels of leptin.²⁸ The combination effect of both diseases on inflammation, oxidative

stress, and the endocrine system has not been comprehensively examined and could lead to greater detrimental effect on the renal function.

There are several limitations in our study. This is a cross-sectional study that shows a significant association between hypoxemia and diabetic nephropathy, but cannot confirm causation. Although we adjusted for several important confounders, we did not take into account others such as smoking and alcohol status. Also, data on albuminuria were not included in the study, which may have missed a greater number of patients with diabetic nephropathy. However, with our current sample of diabetic nephropathy patients, there were still significant associations between AHI and %TST < 90% and eGFR, which suggests that the potential impact of hypoxemia on renal function is likely to be much greater, and we were likely to have underestimated the effect size of the relationship. We also did not assess volume status, as this is difficult to assess accurately based on clinical examination for extremely obese individuals. Our population only includes extremely obese individuals, and the results should be interpreted with care in the general DM population.

This study showed that not only are apnea and hypopnea episodes potentially important in DM nephropathy, but the duration of exposure of nocturnal hypoxemia also appears to play a significant role in the decline in renal function among extreme obese DM patients. There are several implications of the study. Clinicians who manage diabetic nephropathy patients with obesity should be more vigilant in diagnosing as well as treating OSA alongside other cardiovascular modification measures. Further studies should examine the factors mediating the effect of hypoxemia on renal function, and the long-term impact of nocturnal hypoxemia on the progression on DM nephropathy still warrants further investigation.

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