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Effect of CPAP therapy on kidney function in patients with obstructive sleep apnoea and chronic kidney disease: a protocol for a randomised controlled clinical trial

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ABSTRACT

Introduction Obstructive sleep apnoea (OSA) is common in patients with chronic kidney disease (CKD) and may contribute to the progression of kidney disease either through direct effects of hypoxia on the kidney or indirectly through hypoxaemia-induced oxidative stress, endothelial dysfunction, inflammation, activation of the renin–angiotensin and sympathetic nervous systems, and hypertension. Treatment of OSA with continuous positive airway pressure (CPAP) improves many of these physiological abnormalities in patients with normal renal function, though to date there are no trials evaluating the effect of OSA treatment on kidney function in patients with CKD. The purpose of this study is to test the feasibility and efficacy of CPAP therapy in CKD patients with OSA.

Methods and analysis The study is a randomised, controlled, non-blinded, parallel clinical trial in which patients with established CKD are screened for OSA. Patients with OSA are randomised to either conventional medical therapy (control group) or medical therapy and CPAP (CPAP group) and followed for 1 year. The primary outcome is the change in estimated glomerular filtration rate. Secondary outcomes are the change in the urinary albumin/creatinine ratio, the Epworth Sleepiness Scale , Pittsburgh Sleep Quality Index and Kidney Disease Quality of Life questionnaire.

Ethics and dissemination Ethics approval has been obtained from the Conjoint Health Research Ethics Board (ID: REB15-0055). Results from this study will be disseminated through presentations at scientific conferences and publication in peer-reviewed journals.

Trial registration number NCT02420184; Pre-results.

Strengths and limitations of this study

- This is the first randomised controlled trial to evaluate the impact of continuous positive airway pressure on renal function in patients with stage 3 or 4 chronic kidney disease.
- Patients will be recruited from nephrology clinics which make the findings relevant to this patient population and their healthcare providers.
- Although the primary outcome (estimated glomerular filtration rate) and secondary outcomes (albumin/creatinine ratio) are not absolute, such as mortality or need for dialysis, they reflect a change in kidney function that is used in clinical practice.
- This is a single-centre study which may limit its generalisability.

INTRODUCTION

Background and rationale

Chronic kidney disease (CKD) is a global epidemic that affects greater than 10% of adults and the prevalence of CKD continues to increase annually.[1–3] Moreover, CKD increases the risk of cardiovascular morbidity and death,[4] and progression of CKD carries an enormous economic burden.[5 6] The aetiology of CKD includes diabetes, hypertension, glomerulonephritis and obesity,[4 7] but these chronic diseases do not fully explain the increasing prevalence of CKD[8]; furthermore, many patients with CKD progress to end-stage kidney disease (ESKD) despite optimal management of these conditions, highlighting the urgency of identifying novel risk factors and treatments.

Obstructive sleep apnoea is a chronic sleep disorder in which patients stop breathing intermittently during sleep due to closure of the upper airway, leading to nocturnal hypoxaemia and sleep disruption.[9] Sleep apnoea is common (up to 17%)[10] in the general population but the prevalence of OSA in patients with CKD is even higher (up to 40%).[11] Nocturnal hypoxaemia can injure the kidney indirectly through hypoxaemia-induced oxidative stress, endothelial dysfunction, inflammation, activation of the renin–angiotensin (RAS) and sympathetic nervous systems, and hypertension.[12–15] However, nocturnal hypoxaemia

can also damage the kidney directly. The 'chronic hypoxia hypothesis' proposes that damage to the kidney tubule and surrounding interstitium (tubulointerstitial injury) is the final common pathway to ESKD,[16] and nocturnal hypoxaemia associated with OSA may contribute to that pathway.

We have previously reported a significant association between nocturnal hypoxaemia associated with OSA and accelerated loss of kidney function with an adjusted OR of 2.89 (1.25–6.67).[17] We have also shown that OSA is associated with activation of the renal RAS,[18] which may lead to kidney damage by facilitating glomerular and systemic hypertension,[19] and ultimately inflammation and fibrosis[20] within the kidney[21]. Furthermore, treatment of OSA with CPAP reduced renal RAS activity and glomerular hypertension in patients with normal kidney function[22]. These data strongly support the notion that intermittent nocturnal hypoxaemia due to OSA can injure the kidney and contribute to the pathogenesis and progression of CKD. If so, treatment of OSA creates an opportunity to halt or slow the progression of kidney failure.

Two previous studies have explored whether treating OSA with continuous positive airway pressure (CPAP) has an impact on kidney function. Both have been limited by their study design. A retrospective, observational cohort study[23] reported that treatment of OSA with CPAP improved kidney function in patients with CKD. More recently, a randomised controlled trial to evaluate the impact of CPAP on cardiovascular outcomes failed to show any benefit on kidney function[24] but the vast majority of the patients had normal kidney function and the study was not adequately powered to investigate renal outcomes. The purpose of this trial is to evaluate the feasibility and efficacy of CPAP treatment for OSA to slow the loss of kidney function in patients with coexisting CKD, using a randomised, controlled design.

Objectives

The primary objective of the study is to determine whether CPAP therapy will slow the progression of CKD over 1 year. Secondary objectives include an evaluation of whether CPAP therapy improves sleep quality, daytime function and health-related quality of life.

Hypothesis

We hypothesise that in patients with stages 3 and 4 CKD and OSA, adherence with CPAP therapy will:

1. Slow the loss of kidney function reflected by a change in the estimated glomerular filtration rate (eGFR) and the albumin/creatinine ratio[25] (ACR).
2. Improve sleep quality and daytime function reflected by the Pittsburgh Sleep Quality Index[26] (PSQI) and the Epworth Sleepiness Scale[27] (ESS).
3. Improve health-related quality of life reflected by the Kidney Disease Quality of Life[28] (KDQoL) questionnaire.

METHODS AND ANALYSIS

Study design

This study is a randomised, controlled, non-blinded, parallel clinical trial in patients with OSA and CKD that will evaluate the effect of CPAP therapy on kidney and patient-reported outcomes. All patients will be evaluated every 3 months for 1 year to monitor adherence with CPAP therapy, improvement of OSA and nocturnal hypoxaemia, and the change in kidney function and patient-reported outcomes. Figure 1 shows the patient flow.

Study setting

Patients will be recruited from nephrology clinics at the Foothills Medical Centre, in Calgary, Alberta, which are staffed exclusively by kidney specialists and their nursing staff. Patients are referred to these clinics by their primary care physician or other medical specialist for assessment and management of kidney disease and related comorbidities.

Patient recruitment

Adult Patients will be invited to participate in this study provided that they are not currently using CPAP or supplemental oxygen therapy and are able to provide informed consent. Furthermore, they must meet the inclusion criteria listed below:

Inclusion criteria

Inclusion criteria

1. Adult patients (18–76 years).
2. Stage 3 or 4 CKD (eGFR 15–59 mL/min/1.73 m^2).
3. OSA (Oxygen Desaturation Index (ODI)>5) and nocturnal hypoxaemia (oxygen saturation (SaO_2) <90% for greater than 12% of the duration of the home sleep apnoea test (HSAT)).

Exclusion criteria

Exclusion criteria

1. Current treatment with CPAP or supplemental oxygen.
2. Severe daytime sleepiness reflected by an ESS score >15.
3. Commercial driver reporting a recent history of a road traffic incident.
4. Severe nocturnal hypoxaemia reflected by mean SaO_2 <80% on the HSAT.
5. Daytime hypoxaemia reflected by a mean PaO2 of oxygen (PaO_2) <60 mm Hg on an arterial blood gas (ABG)
6. Hypoventilation reflected by awake PaO2 of carbon dioxide ($PaCO_2$) >45 mm Hg on an ABG.
7. Evidence of Cheyne-Stokes respiration (CSR) on the HSAT that accounts for >50% of the estimated RDI.

Education session

All patients who meet these criteria and agree to participate in the study will be identified by a recruiter (ANR) who will obtain informed consent. Following this, a CPAP education and acclimatisation session will be scheduled with a research coordinator (JKR), who will provide a standardised 20 min presentation on OSA and CPAP therapy. The research coordinator will fit

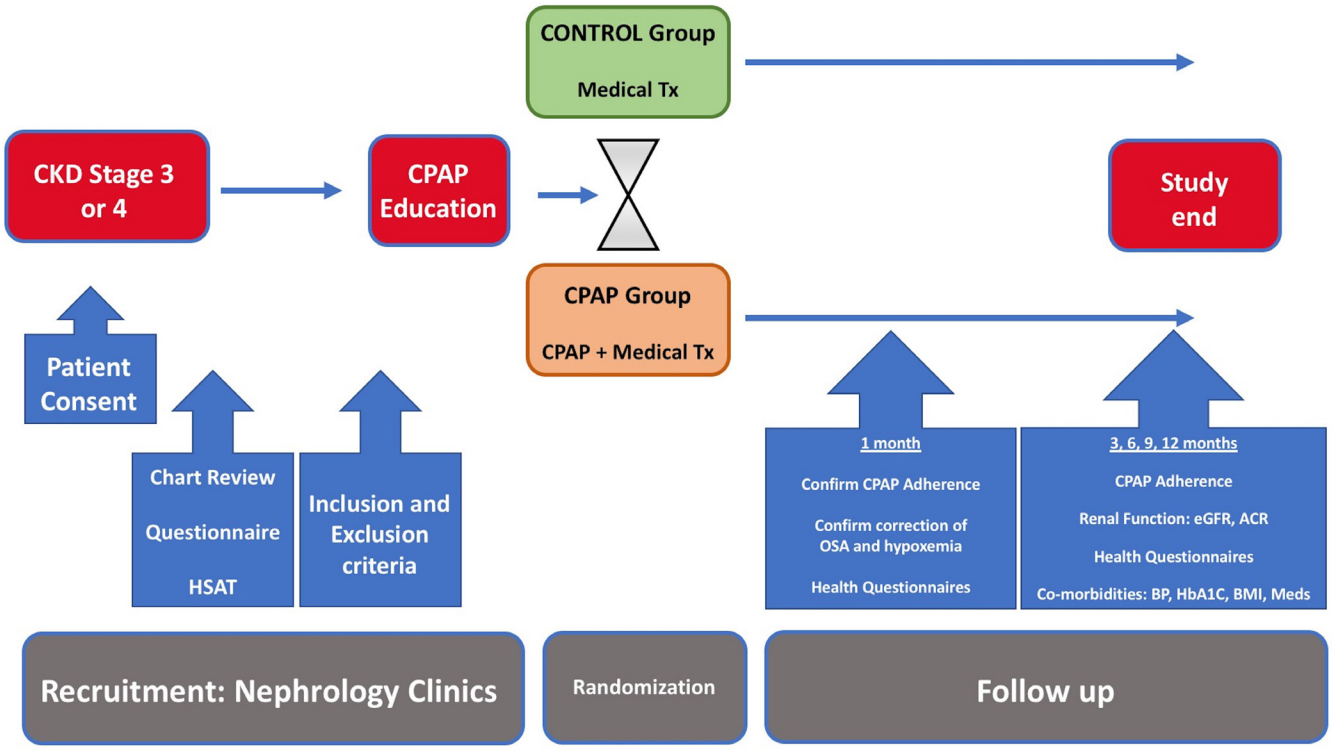

Figure 1 Study protocol. ACR, albumin/creatinine ratio; BMI, body mass index; CKD; chronic kidney disease; CPAP, continuous positive airway pressure; eGFR, estimated glomerular filtration rate; HSAT, home sleep apnoea test; OSA, obstructive sleep apnoea; BP, Blood Pressure; HbA1C, Hemoglobin A1C

the patient with a comfortable interface (mask) and show them how to use a CPAP unit set at a pressure of 4 cmH_2O.

Randomisation, allocation concealment and blinding

Following the education session, patients stratified by stage 3 and stage 4 CKD will be randomly allocated equally (1:1) to receive either usual medical treatment for CKD (control group) or usual medical treatment with CPAP (CPAP group). Randomisation will be done using a web-based system (http://www.randomization.com) which will provide the research coordinator with the patient's assignment. Randomisation will be performed by means of a random number generator for an initial block of 20 patients for stage 3 CKD and 20 patients for stage 4 CKD. For further recruitment, to ensure even allocation, randomisation will occur in blocks of 6 for each CKD stage strata. To ensure allocation concealment, we will follow a stringent procedure to ensure enrolment before randomisation. Recruitment and randomisation will be performed by different individuals, as outlined above, and without the involvement of other investigators. The allocation will be concealed and will be broken by the research coordinator only after the participant has met all selection criteria and completed the education session. Neither the patients nor the research staff will be blinded to the intervention (CPAP) or medical treatment for CKD.

Intervention

Patients randomised to receive CPAP will be referred to a respiratory homecare company in Calgary for CPAP initiation. All patients will be started on auto CPAP (15/5 cmsH2O). The effectiveness of auto CPAP will be reviewed on the first CPAP download, 1 month after randomisation and the accompanying HSAT. If the patient's apnoea and hypoxaemia are satisfactorily controlled, the patient will remain on those auto CPAP settings. However, if the patient has persistent hypoxaemia or apnoea, appropriate changes will be made such as adjustment of the auto CPAP setting or conversion to fixed CPAP. The HSAT test will be repeated until CPAP efficacy has been optimised. The patient will remain on whichever CPAP mode and settings works best to control their apnoea and nocturnal hypoxaemia. The CPAP units have been provided for the study by Philips Respironics (REMstar Auto A-flex with humidifier). Following 1 year of CPAP therapy, the CPAP unit will be returned to the research coordinator for use by other patients recruited to the study. Patients are given the option to purchase a CPAP machine after completion of the study.

Data collection

HSAT with the Remmers Sleep Recorder (RSR: Model 4.2, Saga Tech Electronics, Calgary, Alberta, Canada) will be used to identify OSA and nocturnal hypoxaemia in patients with CKD. This technology has been

validated[29] and used in previous research studies in this patient population[30]. It consists of an oximeter to record arterial oxygen saturation and heart rate, a pressure transducer to record nasal airflow via nasal cannula, a microphone to record snoring and a body position sensor. The following indices will be used to quantify the severity of nocturnal hypoxaemia: (1) ODI, based on a 4% oxygen desaturation, (2) mean SaO_2 (average SaO_2 during the entire recording) and (3) the duration of SaO_2 <90% during the recording.

Patients will be instructed how to use the monitor for a single overnight study in their home. The raw data will be reviewed by a sleep medicine physician (PJH) to determine that the HSAT is technically satisfactory by meeting both of the following criteria: (1)>5 hours of monitoring over a single night, (2) quality of oximetry and airflow recordings sufficient to detect the presence of OSA. If the study is not technically adequate, or if the patient reports sleeping for less than 50% of the time that the monitor was worn, he/she will be asked to repeat the study and will be excluded if they decline or if the repeat test is not technically satisfactory. Review of the raw data will confirm that episodes of intermittent oxygen desaturation are due to apnoea and whether apnoea is central CSR) or obstructive (OSA), based on the morphology of the airflow recordings.

As outlined above, the HSAT will be used to confirm correction of OSA and nocturnal hypoxaemia by repeating the test on CPAP therapy. In addition, patients will be asked to repeat the HSAT at the end of the study to determine if their OSA has changed (control group) or to confirm that their CPAP therapy remains effective (CPAP group). These data will provide the opportunity to compare variability in the efficacy of CPAP on renal outcomes.

CPAP adherence will be monitored by electronic download from the CPAP unit. Satisfactory CPAP adherence will be defined a priori as CPAP use for >4 hours/night on >70% nights for the preceding 4 weeks[31]. Furthermore, CPAP adherence will be quantified for each of these months as the number of hours CPAP was used each day Any adverse events related to CPAP therapy will be recorded.

Kidney function will be measured at the time of randomisation (baseline) and at each 3-month follow-up visit by measurement of eGFR and albuminuria. Estimated GFR will be based on serum creatinine values incorporated into the Chronic Kidney Disease Epidemiology (CKD-EPI) equation[32] and albuminuria will be measured using the ACR. The time of these measurements will be determined by patient availability.

Additional measurements recorded at baseline and at each follow-up visit include the following: body mass index (BMI), blood pressure, comorbidities, medications (with particular attention those that may alter renal outcomes such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), questionnaires (ESS, PSQI, KDQoL) and hemoglobin A1C (HbA1C) (if the patient has diabetes). Lastly, the aetiology of CKD is determined at baseline. The data collection points are summarised in table 1.

Outcomes

Primary outcome

eGFR: The primary outcome of the study is the change in eGFR calculated from measurement of serum creatinine and use of the CKD-EPI equation. The absolute change from baseline in the control group and CPAP group will be analysed at 6 months and 12 months and the difference in the rate of change between each group will be analysed at predetermined time points (3, 6, 9 and 12 months after randomisation). eGFR was chosen as the primary outcome for many reasons. First, eGFR is used in the clinical management of patients with CKD for prognosis and to optimise care.[25] Second, measurement of eGFR is readily available through measurement of serum creatinine. Third, loss of kidney function as measured by eGFR is a common outcome measurement in studies that have evaluated other therapies for CKD[33 34]; hence the impact of CPAP on kidney function can be compared with the effect of other disease-modifying therapies.

Secondary outcomes

A number of secondary outcomes will be measured at 3, 6, 9 and 12 months after randomisation to determine the efficacy of CPAP treatment on proteinuria, sleep-related symptoms and quality of life:

- ACR: Urinary albumin excretion is associated with cardiovascular risk and mortality[35 36]. This will be measured at the same predetermined time points as eGFR.
- PSQI: The PSQI is a validated, self-reported questionnaire that measures subjective sleep quality by asking patients about difficulties initiating and maintaining sleep. A score greater than 5 (out of 9) indicates poor sleep quality.
- ESS: The ESS is a self-reported questionnaire that measures subjective sleepiness. Patients are asked to rate the tendency to fall asleep in eight passive situations. The overall score is out of a total of 24, with scores greater than 10 considered abnormal.

  KDQoL: The KDQoL focuses on the health concerns of patients with CKD. This has been modified slightly, by omitting two questions that ask about dialysis, to make it suitable for the non-dialysis CKD population. Each of the 21 remaining questions is scored separately in the following manner. Each qualitative response is converted to a precoded numeric value which is then transformed to a range of 0–100, with a higher value representing a better quality of life. Scores represent a percentage of the total possible score. If there are multiple items in the same question, the scores for each item are averaged together to create a single score for that question[37].

Table 1 Data collection points

	Baseline	1 month	3 months	6 months	9 months	12 months
OSA						
HSAT	√	√				√
CPAP download		√	√	√	√	√
Kidney function						
eGFR	√		√	√	√	√
ACR	√		√	√	√	√
Questionnaires						
ESS	√	√	√	√	√	√
PSQI	√		√	√	√	√
KDQoL	√		√	√	√	√
Anthropomorphics						
BMI	√		√	√	√	√
BP	√		√	√	√	√
Miscellaneous						
Comorbidities	√					
Meds	√		√	√	√	√
HbA1C	√		√	√	√	√

ACR, albumin/creatinine ratio; bmi, body mass index; CPAP, continuous positive airway pressure; eGFR, estimated glomerular filtration rate; ESS, Epworth Sleepiness Scale; HSAT, home sleep apnoea test; KDQol, Kidney Disease Quality of Life; OSA, obstructive sleep apnoea; PSQI, Pittsburgh Sleep Quality Index; BP, Blood Pressure; HbA1C, hemoglobin A1C.

Feasibility of this study design

We will assess the feasibility of this study design by measuring the following additional outcomes:

- Number of patients who decline to have a HSAT when this is offered to them in the outpatient clinic.
- Number of patients who decline CPAP therapy following randomisation.
- Number of patients whose adherence with CPAP therapy is inadequate (defined as CPAP use <4 hours/night, averaged over 12 months).

Sample size and statistical analysis

The absence of previous randomised studies to evaluate the use of CPAP for OSA in patients with CKD poses a challenge when estimating the sample size required for this study. Consequently, a convenience sample of 60 patients with CKD (30 with stage 3 CKD and 30 with stage 4 CKD) with OSA and nocturnal hypoxaemia will be enrolled.

Data will be expressed as mean ±SEM, median/IQR or proportions, as appropriate. The primary outcome of a change in eGFR will be assessed as a continuous variable. Multiple repeated measures t-test will be performed to compare the change in eGFR associated with treatment of OSA at each time point between the CPAP group and control group. Furthermore, patients who progress to dialysis or experience a rapid decline in renal function within the 12-month trial will be reviewed to determine if there was an acute event that was responsible for this rapid progression. If we find evidence of a significant kidney injury over and above what might be expected from nocturnal hypoxaemia, we will assess the impact of this on our results. Mixed analysis of variance (ANOVA) will be performed to compare the change in kidney function over time between the CPAP group and control group. Since mixed ANOVA is an omnibus test statistic and cannot determine at which specific time points (baseline, 3 months, 6 months and 12 months) kidney function has changed, post hoc tests will be performed to determine that. A 'last observation carried forward' imputation method will be used to deal with missing values. Our primary assessment will use intention-to-treat analysis as it is more conservative, and will reduce the chance of a type 1 error. However, data will be also analysed as per protocol, and as treated, to explore the potential impact of CPAP therapy on renal outcomes and to provide pilot data for planning a larger clinical trial.

The secondary outcome is the change in ACR from baseline to both 6 and 12 months in both the CPAP and control groups. Students t-tests will be performed to determine if the change from baseline and between groups is significant. Two-sample Wilcoxon rank sum tests will be used to analyse the change in ESS, PSQI and KDQoL in both groups from baseline to 12 months. The two-sample Wilcoxon rank sum test is used to determine if there is a difference in the median perceived health quality in ranked data.

All outcomes will be assessed for possible effect modification or confounding effects from BMI, diabetes and

hypertension through stratified analysis. Furthermore, covariates such as aetiology of disease, gender, severity of kidney disease, CPAP adherence and severity of sleep apnoea will also be assessed.

All statistical analysis will be performed using STATA statistical analysis software program(STATA V.15, StataCorp LLC) statistical significance will be assumed at $p<0.05$.

Patient and public involvement

Patients and the public were not involved in the development of this research protocol

TRIAL MANAGEMENT

Following initial approval, the study is reviewed annually. Any modification of the study protocol requires a formal application and approval by the ethics board.

Updates of the study protocol are required at least every 12 months. The principal investigator is responsible for reporting adverse events and any other unintended consequences of the trial.

Trial status

Patient recruitment began in July 2015 and is ongoing. We anticipate completion of the study by August 2019.

Data quality and management

All data will be stored on a secure network behind a firewall at the University of Calgary. All data will be accessed and analysed solely by the principal investigator and his research team using password-protected computers. Patient identifying information will be replaced with unique identifiers for any data seen by individuals other than the principal investigator and research assistants. Paper copies of unique identifiers are locked in a cabinet in a locked office and all electronic identifiers are behind the Alberta Health Services firewall in a password-protected document.

The trial steering committee consists of PJH, SBA, SRP and TCT. We do not feel that a formal committee for data safety and monitoring is required since the intervention in our trial (CPAP therapy) has minimal risk and our sleep centre and the CPAP providers in the community have extensive experience with this treatment. Furthermore, our exclusion criteria were chosen to avoid recruitment of patients in whom CPAP therapy may not be appropriate.

Consent and withdrawal

Patients will be recruited by a research assistant who is not involved in the clinical management of their OSA or CKD. Written informed consent will be obtained from the patients prior to taking part in the study. The research assistant will coordinate collection of all data including the primary and secondary outcome data. Participants may withdraw from the study at any time and without any consequences. If a patient chooses to change treatment by discontinuing or starting CPAP, they will be asked to continue to contribute their outcome data to the trial. If they choose not to participate further, data obtained up to the time of withdrawal will be retained but no further data will be collected.

Dissemination

Results will be disseminated though presentations at local, national and international scientific meetings and in peer-reviewed publications. In addition, the research will be shared with the sleep medicine community through the knowledge translation infrastructure that has been established in the Canadian Sleep and Circadian Network (www.cscnweb.ca), and with the nephrology community through Canadian Society of Nephrology and Alberta Health Services Kidney Strategic Clinical Network.

DISCUSSION

CKD is common, and its prevalence is increasing.[1–3] This has important implications both for individual patients and the healthcare system. First, CKD has been shown to be an important medical morbidity, which increases the risk of adverse clinical outcomes.[2 4 7] Second, progression of CKD to ESKD increases morbidity and mortality and carries an enormous financial burden.[5 6] Consequently, it is important that new and innovative strategies be considered that will help to prevent the development of CKD and/or delay its progression to ESKD. Diabetes mellitus and systemic hypertension are common causes of CKD but, not infrequently, optimal medical therapy for these conditions does not prevent the development of CKD or its progression.[4 7 8] OSA is commonly found in patients with CKD and there are several plausible biological mechanisms through which untreated OSA may harm the kidney[11 19 38].

Basic experiments in isolated animal preparations have shown that the healthy kidney is susceptible to adverse physiological changes such as enhanced sympathetic activation in a simulated hypoxic environment[39 40]. Whole animal models of intermittent hypoxaemia that mimic OSA (even without the accompanying sleep disruption and changes in intrathoracic pressure that characterise OSA) have shown that hypoxaemia can cause cell death and fibrosis resulting in impaired kidney function[41]. In humans, CPAP therapy has been shown to correct the impaired renal haemodynamics associated with OSA and accompanying nocturnal hypoxaemia.[22] Finally, OSA has been associated with an increased risk of developing CKD in several large studies[42]. Although this work supports the concept that OSA is an important risk factor for the development and progression of CKD, the hypothesis remains unproven without an appropriate intervention study.

Notwithstanding the limitations of CPAP therapy, it remains the single most effective intervention for the treatment of OSA. A randomised controlled trial that evaluates the impact of CPAP on renal function in patients with OSA may help to identify new therapeutic strategies. If CPAP does benefit the kidney, the patient population

with the most to gain would be those with coexisting CKD. Consequently, the ideal target population for this research are those patients with both CKD and OSA. This is a large population since the prevalence of CKD is high and concomitant OSA is found in up to 40%[11].

Although a large multicentre trial may be required to definitively address this important question, a smaller trial, such as ours, is initially required for a number of reasons. Since OSA is asymptomatic in many patients with CKD[43], accurate detection will require diagnostic sleep testing. It is important to determine whether this additional testing is acceptable for patients who already have significant medical issues. To address this, we will record the number of patients who decline HSAT testing when it is offered to them in clinic. Second, treatment with CPAP can be challenging, particularly, if the patient does not perceive symptomatic benefit. Consequently, it is important to have initial data on CPAP adherence in this patient population. To address this, we will also look at the number of patients that decline or discontinue CPAP therapy following randomisation and CPAP education as well as the overall adherence with CPAP therapy. Third, if CPAP does improve kidney function, this may require several months to manifest itself. Patients randomised to a treatment arm without CPAP will need to go without active treatment for their OSA for several months. In our opinion, this is justifiable since we have excluded patients with severe OSA symptoms such as excessive sleepiness and there is currently no evidence that withholding CPAP therapy will hasten the decline in kidney function. However, it is not clear if withholding CPAP from patients who have received a diagnosis of OSA will be acceptable to them. Consequently, we will identify the number of patients who decline to join the control group for this reason. We will address the impact of withholding CPAP by identifying the number of patients who experience a significant decline in kidney function when CPAP therapy is withheld for the course of the study (ie, the control group). We will try to mitigate this risk by offering all patients CPAP therapy at end of study regardless of treatment designation. Finally, a pilot study such as this can also provide sufficient data on which to calculate a sample size for a larger, multicentre trial.

Limitations

The proposed study has some limitations. First, eGFR and ACR have intrinsic variability that may confound our ability to detect a change between the CPAP and control groups. Since we are recruiting patients with established CKD, many of them will have had previous measurements of eGFR and ACR, which we can access. Analysis of this data will provide a measurement in each patient of the variability in these indices of kidney function over several months prior to enrolment. Patients with high variability in eGFR and ACR prior to enrolment may respond differently to CPAP than those with low variability Although these measures of variability will not be used in our formal statistical analysis, we will investigate this possibility with an exploratory analysis by comparing the response to CPAP between those with high and low variability in eGFR and ACR prior to enrolment. In addition, we have several measurements of eGFR and ACR after enrolment, which will reduce the chance of a single sporadic change confounding our analysis.

Second, this is a small, single-centre study, which may limit generalisability. However, the clinics from which we will recruit are attended by a large group of nephrologists with variable clinical practices, and Calgary is a large city that serves a diverse, multiethnic population. Our small sample size will limit the power of our statistical analysis. However, this is a pilot study to obtain preliminary data on which to determine if a larger study is feasible and to inform study design. In addition, our results will not be generalisable to the full spectrum of CKD since we are only recruiting patients with CKD stages 3 and 4. Our rationale for this recruitment strategy was to avoid both those with mild CKD that is unlikely to change over 12 months and patients with stage 5 CKD whose disease may be irreversible.

Third, the length of the follow-up increases the potential for a significant number of drop-outs and falling adherence with CPAP therapy, which could bias our results. We will address this with our statistical analysis by including CPAP adherence as a modifying factor in the primary and secondary outcomes, and by gathering detailed information on those that drop-out so that we can compare them to those that remain in the study. Our analysis may provide important insight into predictors of poor CPAP adherence in this population, which can be incorporated into the design of a larger study. We are attempting to limit drop-outs by including an education session and frequent follow-up.

Contributors PJH, SBA, TCT and SRP contributed to the study concept and design. TCT provided statistical expertise and analysis. JKR, EJL and ANR contributed to patient recruitment and data acquisition. ANR and PJH wrote the initial draft of the manuscript and all authors have reviewed, revised and approved the final version.

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Disclaimer This is an investigator-initiated study and the sponsors have no role in the design or execution of the study, or in the dissemination of the results.

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval The study was reviewed by the Conjoint Health Research Ethics Board at the University of Calgary to ensure that its content and procedures were compliant with research standards and regulations (ID: REB15-0055).

Provenance and peer review Not commissioned; externally peer reviewed.

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