

# Parathyroidectomy improves the quality of sleep in maintenance hemodialysis patients with severe hyperparathyroidism

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## ABSTRACT

Sleeping disorders are very common in patients with chronic kidney disease on dialysis (CKD<sub>5D</sub>) and are an emerging risk factor able to predict mortality. Parathyroid hormone (PTH) although considered a pivotal uremic toxin has rarely been associated with sleep disorders in uremia. In a study from our laboratory PTH concentrations failed to distinguish patients with sleep disorders from those without. In a study performed by Chou et al a 97% prevalence of insomnia was found in patients undergoing hemodialysis requiring parathyroidectomy. Surgery reduced PTH and increased sleeping hours within 3 months. The aim of this study was to study the effects of parathyroidectomy on the sleep disorders of insomniacs on maintenance hemodialysis. The study was performed in 16 insomniac patients on maintenance hemodialysis who successfully underwent surgery with autotransplantation of autologous parathyroid tissue (40 mg) under the skin of the forearm. Patients (5 F and 11 M) were studied from 1 month before surgery to 1 year after. Sleep disorders were assessed by means of a 27-item questionnaire - Sleep Disorder questionnaire (SDQ) - that identified sleeping disorders according to Diagnostic and Statistical Manual of Mental Disorders - IV Edition (DSM-IV) criteria. The Charlson Comorbidity Index (CCI) was also measured along with systolic and diastolic blood pressure, Hb, PTH, Ca, P. A 95.5% prevalence of sleep disorders was found pre operatively. Patients slept  $4.90 \pm 1.2$  hours, Ca averaged  $10.09 \pm 0.54$  mg/dL, Phosphate  $5.5 \pm 1.93$ , CCI  $9.8 \pm 1.1$ , PTH  $1498 \pm 498$  ng/mL. After 1 year follow-up 2 out 16 patients had normal sleep, 6 out 16 patients had subclinical sleep disorders and 8 remained insomniacs ( $p=0.008$ , Mc Nemar Test for paired data, insomniacs vs. no disturbance + subclinical disorders). Sleeping hours increased up to  $6.0 \pm 1.24$  ( $p<0.05$ ), PTH was normalized, the Charlson Comorbidity Index was reduced ( $p<0.05$ ) as were plasma calcium and phosphate ( $p<0.01$ ). The study indicates that insomnia in patients with severe hyperparathyroidism on maintenance hemodialysis is ameliorated by parathyroidectomy.

**Key words:** PTH, Hyperparathyroidism, Hemodialysis, Parathyroidectomy, Insomnia, Sleep disorders

## INTRODUCTION

Sleeping disorders affect 41-85% of patients with end stage renal disease undergoing hemodialysis and are an emerging risk factor able to predict mortality (1). There are many putative reasons for sleeping disorders including a stressful life, anemia, abnormal blood urea, blood gases, plasma creatinine, elevated blood pressure, the morning dialysis shift (2-10). Since 1986 Kimmel et al have maintained that blood urea and creatinine plasma concentrations could not explain sleep disorders (11). Such findings have been confirmed in many studies (12, 13).

PTH although considered a pivotal uremic toxin (14), has rarely been investigated in studies focussing on sleep disorders in patients with end-stage kidney disease. However in a recent study performed in Taiwan Chou et al (15) reported a 97% prevalence of sleep disturbances in patients with severe symptomatic secondary hyperparathyroidism waiting for parathyroidectomy. The study also showed that 3 months after parathyroidectomy quality and quantity of sleep ameliorated. In addition, in a recent review Parker (8) was inclined to attribute a role to PTH in sleeping disorders in uremic patients since elevated PTH hormone concentrations have neurotoxic effects (16), and have also been associated with increasing waking electroencephalograms slow wave activity in uremic animals (17) and in stable dialysis patients (18).

In order to further explore the link between PTH concentrations and sleep disorders we decided to prospectively study insomniac hemodialysis patients for 1 year after parathyroidectomy for incompressible hyperparathyroidism by means of a specific questionnaire. Data will be presented indicating that in such patients 1 year after the operation insomnia is ameliorated.

## PATIENTS AND METHODS

### Patients

A total of 16 insomniacs (5 women and 11 men) on maintenance hemodialysis (Tab. I) needing parathyroidectomy for secondary hyperparathyroidism being dialyzed 3 times a week for a total of 12-14 hours were prospectively enrolled for this study. They had been treated with various phosphate binders, appropriate concentration of calcium in the dialysate, and ate diets providing 1g of protein /kg of body weight, mainly rice and fish. The characteristics of the patients at time of the study are listed in Table I. The enrolment was restricted to insomniacs in order to follow-up patients with the worst sleep. Only 3 patients were taking sleeping pills. The sparing use of hypnotics reflects a local attitude of family physicians.

### Parathyroidectomy

Total parathyroidectomy was associated with autotransplantation into the forearm of the non dominant arm. To this end slices of parathyroid gland (40 mg in total) are implanted in multiple pockets in muscle on the lateral aspects of the flexor surface. Non absorbable suture is used to secure the slices in the muscle pockets and to provide a marker in case surgical resection is necessary (14, 19). Post operatively oral calcitriol and oral calcium carbonate were given to keep the patients free of tetany and to secure a serum calcium concentration above 8 mg/dL.

### Assessment of sleep disorders

Sleep disorders were assessed pre operatively and 12 months later by means of a 27-item questionnaire SDQ (19) which identifies sleeping disturbances according to DSM IV criteria. SDQ provides a hierarchical classification for relevant insomnia, relevant hypersomnia, subclinical insomnia or the absence of sleep complaints. The criteria adopted were the frequency, the persistence and relevance of the disturbance indicated by the DSMIV and by the International Classification of sleep disorders R (ICSDR). A specific question on the SDQ concerns the description and consumption of hypnotics. The SDQ represents a valid instrument for assessing the incidence of sleep disorders in epidemiological studies and for diagnostic screening because of its clarity, rapidity and validity.

We have used the SDQ in previous studies on hemodialyzed patients (20, 21). Patients were also required to indicate the amount of time they slept before and after dialysis treatment as well as the number and average length of naps over a weekly period.

### Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) is a composite score of multiple co-morbid conditions and age (22). Co-morbid conditions are given a score of 1 to 6. The CCI assigns 1 point to myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular diseases, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, and diabetes without end organ damage. Two point are assigned to hemiplegia, moderate or severe renal disease,

**TABLE I**  
CHARACTERIZATION OF 16 INSOMNIACS ON MAINTENANCE HEMODIALYSIS 1 MONTH BEFORE PARATHYROIDECTOMY

#### Characterization of patients

No.	16
Age, years	54.6±13
Gender	11 M/5 F
Dialysis, months	70±8.92
Body weight, kg	62±10
BMI	24.0±2.73
Plasma albumin, g/dL	4.64±1.3
Hemoglobin, g/dL	12.3±1.08
Blood urea, mg/dL	206±19
Creatinine, mg/dL	9.8±1.7
iPTH, ng/mL	1434±400
Ca, mg/dL	10.09±0.54
Phosphate, mg/dL	6.4±1.75
Bone pain	4.0±1.1
SBP, mm Hg	137.9±13.48
DBP, mm Hg	82.7±11.06
Antihypertensive drugs	16 out 16 (100%)
Charlson Comorbidity Index	9.4±1.0
Sleeping hours	5.08±1.4
Daily naps	1.9±1.6
Sleeping pills	3 out 16 (18.7%)

Data are given as mean ± SD.

diabetes with end organ damage, tumor without metastasis, acute and chronic leukemia, lymphoma. A total of 3 points are assigned to moderate or severe liver disease whereas 6 points are assigned to metastatic solid tumors and AIDS. Finally for each decade above 40 years of age a score of 1 is added. For hemodialyzed patients the minimum CCI is 2. The 16 patients in this study had a high Comorbidity Index score (Tab. I).

Pain was assessed by item no. 7 of SF-36 (Italian version 1.5).

### Blood pressure control

Predialysis systolic and diastolic arterial pressure (3 measurements on 3 consecutive dialysis days) was obtained 1 month before the operation. The use of antihypertensive drugs was also registered for each individual patient. All of them were on a combination of antihypertensive medications (betablockers, Calcium channel blockers, ACEi, ARB receptors antagonists).

### Analytical methods

Serum levels of urea nitrogen, creatinine, albumin, calcium, phosphate and hemoglobin were measured by auto-analyzer. iPTH was measured by chemiluminescence using Sorin kit sets (Saluggia, Italy). Alkaline phosphatase was evaluated enzymatically.

### Data analysis

Data are given as mean  $\pm$  SD. Statistical significance was assessed by t paired test for parametric data and by Wilcoxon signed rank test for non parametric data. No patients had excessive daytime sleepiness so they were divided into 3 groups for statistical analysis according to the SDQ score: patients without a sleep problem (No), patients complaining of subclinical sleep disorders (Sub) and patients complaining of insomnia (I).

## RESULTS

Parathyroidectomy significantly improved quality of sleep. As indicated in Table II after 1 year only 50% of the patients were still insomniacs, 37.5% had subclinical sleep disorders and 2 (12.5%) had normal sleep ( $p=0.008$ , Mc Nemar Test for paired data, insomniacs vs. no disturbance + subclinical disorders). None used sleeping pills. One year after operation an increase was observed in sleep duration ( $6.0 \pm 1.24$  versus  $4.90 \pm 1.2$  hours,  $p<0.05$ ) and daily naps (from  $1.9 \pm 1.16$  vs  $4.9 \pm 3.03$ ,  $p<0.01$ ), as indicated in Table III.

One year after the operation there was a statistically significant reduction of iPTH, calcium, phosphate and alkaline phosphatase. Also the number of patients with itching, weakness and bone pain decreased significantly (Tab. IV). Following parathyroidectomy blood pressure control

**TABLE II**  
FOLLOW-UP CHANGES IN QUALITY OF SLEEP IN INSOMNIACS

	No disturbance	Insomniacs	Subclinicals disorders
Baseline	0%	100% (16)	0%
12 months	12.5% (2)	50% (8)*	37.5% (6)

\*  $p=0.008$  for insomniacs vs. no disturbance + subclinical disorders.  
In parentheses the number of patients.

**TABLE III**  
SLEEPING DISTURBANCES IN 16 INSOMNIACS ON MAINTENANCE HEMODIALYSIS 12 MONTHS AFTER OPERATION

	Baseline	12 months	p
Sleeping hours	$4.90 \pm 1.2$	$6.0 \pm 1.24$	0.05
Naps	$1.9 \pm 1.16$	$4.9 \pm 3.03$	0.01

improved, only 12 out 16 patients needed antihypertensive treatment. The Charlson Comorbidity index was very high before parathyroidectomy and fell significantly after the operation (Tab. IV).

## DISCUSSION

Hemodialyzed patients with severe hyperparathyroidism had improved sleep 12 months after successful parathyroidectomy. Fifty per cent of them switched from insomnia to subclinical sleep disorders whereas in 12.5% a normal sleep was restored. The operation was associated with an increase in sleeping hours and of daily naps, bone pain and biochemistries improved and Charlson Comorbidity Index was reduced. The fact that the number of daily naps increased after the operation along with the sleeping hours is relevant since it indicates an improvement in quality and quantity of sleep.

The data confirm and extend the findings of Chou et al, who worked with patients with a comparable level of hyperparathyroidism, and reported an improved sleep 3 months after parathyroidectomy in a group of patients who had less disturbed sleep at baseline. The improvement was explained

by a decrease of symptoms such as itching, bone pain and general weakness (15). In this respect, present data also suggest a role for the improved Charlson Comorbidity Index which is higher than in other studies done in our laboratory (20). The data indicate that the beneficial effects of successful parathyroidectomy on sleep disorders are long lasting and occur also in the worst sleepers (the insomniacs).

Present results as well as those of Chou et al (15) have been obtained in patients with severe hyperparathyroidism, insuppressible by usual medical procedures and requiring surgery, so they cannot be extrapolated to the less severe forms of renal hyperparathyroidism. This caveat emerges from data in a previous study from our laboratory where PTH concentration did not discriminate between absence of sleep disorders, subclinical disorders or insomnia. However, in that study mean PTH concentration was the lowest in patients with no sleep disorders and highest in those with insomnia (5). Unfortunately there is little data in the literature on the effects of successful medical therapy on sleep disorders of patients on dialysis or with progressive chronic kidney disease.

Plasma calcium concentration might have a causative role for sleep disorders in the patients enrolled for this study, since occasional or constant insomnia was linked to

**TABLE IV**  
EFFECTS OF PARATHYROIDECTOMY IN 16 INSOMNIACS ON MAINTENANCE HEMODIALYSIS

	1 month before surgery	12 months after surgery	p
PTH, ng/mL	1434±400	40.3±37.4	0.0001
Ca, mg/dL	10.09±0.54	8.89±0.88	0.01
P, mg/dL	6.4±1.75	4.95±1.31	0.05
Total alkaline phosphatase, u/L	424±345	97±44	0.01
Bone pain	4.4±1.1	2.2±0.9	0.01
SBP, mm Hg	138.9±18.39	130.8±23.47	0.05
DBP, mm Hg	83.1±11.84	78.8±6.70	0.05
Antihypertensive drugs	16 out 16	12 out 16	
Hb, g/dL	12.1±0.90	12.41±0.78	
Albumin, g/dL	4.55±0.66	4.59±0.76	
Cholesterol, mg/dL	170±32	183±44	
Charlson Comorbidity Index	9.4±1.6	7.4±1.3	0.05
Itching	10	4	0.001
General weakness	10	5	0.001
Bone pain	15	4	0.001
Sleeping pills	3	0	

Patients completed 1 year follow-up following the operation, the graft was functioning. Table compares data collected at the times of decision for surgery and data obtained 12 months after successful therapy.

hypercalcemia by Argiles et al (23) and by Virga et al (24, 25), in studies where patients had calcium concentrations below those measured in present experiments.

In conclusion present findings strongly suggest that PTH might have a causative role for sleep disorders in severe renal hyperparathyroidism since parathyroidectomy improved the quality of sleep in 50% of the patients. The data also suggest the need to explore the effects of successful medical therapy on sleep disorders in CKD grade 3-4 as well as in patients in maintenance hemodialysis with less severe hyperparathyroidism, treated with different pro-

ocols of PTH suppression, a goal which is now possible due to the availability of drugs with different mechanisms.

Conflict of interest statement: None declared.

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