Nephrol Dial Transplant (2008) 23: 336–344
doi:10.1093/ndt/gfm559
Advance Access publication 22 September 2007

Original Article

NDT
Nephrology Dialysis Transplantation

Haemodialysis patients with sleep apnoea syndrome experience increased central adiposity and altered muscular composition and functionality

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Abstract

Background. Sleep apnoea frequently affects patients with end-stage renal disease. However, it is still unclear whether or to what extent sleep disorders may affect functional capacity and quality of life in haemodialysis patients. We tested the hypothesis that apneic dialysis patients due to the lack of restorative sleep will have a further reduced functional capacity and further compromised quality of life compared to their non-apneic counterparts.

Methods. Forty-three clinically stable haemodialysis patients (13 F, 56.6 ± 19.4 years) were examined. After polysomnographic analysis, patients were divided in two groups according to their calculated apnoea hypopnoea index (AHI; cutoff 5). Primary outcomes were intergroup differences in the following: (1) physical capacity and muscle performance, assessed by functional tests, (2) quality of life, assessed by the SF-36, (3) body composition, measured by DEXA and (4) muscle composition and size, as well as (5) visceral (VAT) and subcutaneous (SAT) adipose tissue, calculated by computed tomography.

Results. Twenty-two patients had AHI >5 (4 F, AHI = 28.8 ± 22.3). The adjusted analysis for age, BMI and years in dialysis therapy, showed that the low-AHI group ($N = 21$, 9 F, AHI = 1.8 ± 1.3) had better functional capacity, and performed better in muscle strength and endurance tests compared to the high-AHI group. There were no differences in lean body mass and % total body fat between groups, however, values for VAT, VAT/TAT ratio and thigh muscles' fat infiltration were increased in the high-AHI group. VAT correlated with BMI ($r = 0.682$, $P = 0.001$), functional capacity ($r = 0.558$, $P = 0.001$) apnoea hypopnoea index ($r = 0.530$, $P = 0.001$). There were no statistical significant differences in quality of life between the two groups. To further account for age and BMI differences, a subgroup of patients was matched by age, sex and BMI ($N = 10$/group). In the matched analysis, all the above statistical differences remained, between the low-AHI and high-AHI groups.

Conclusions. Haemodialysis patients with sleep apnoea syndrome demonstrate poorer functional capacity, physical performance and muscle composition, compared to non-apneic dialysis patients. Overall, sleep apnoea appears to partly contribute to the total diminished functional capacity of haemodialysis patients.

Keywords: fat infiltration; haemodialysis; lean body mass (LBM); muscle functional capacity; obstructive sleep apnoea–hypopnoea syndrome; visceral adipose tissue

Introduction

Sleep disorders affect 2–4% of the middle-aged adults in the general population [1] and, are commonly associated with increased morbidity and mortality rates [2]. The prevalence of sleep apnoea syndrome in

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haemodialysis patients is at least 10 times higher [3] than those values reported in the general population [1].

Sleep apnoea disorders are characterized by insufficient quantity and quality of restorative sleep, impaired daytime functioning, tiredness and fatigue that lead to a significant reduction in the quality of life (QoL) [4,5]. In the haemodialysis population more than 50% of patients complain at some point of sleep-related symptoms such as insomnia, sleep apnoea, fatigue and restless legs syndrome [6,7], however until now it is not known whether these symptoms are due to haemodialysis-induced uremic myopathy or due to the chronic lack of restorative sleep.

The pathophysiology of haemodialysis-related obstructive sleep apnoea–hypopnoea syndrome (OSAHS) remains obscure, however, a strong body of evidence suggests that uraemia-related factors are responsible for the prevalence of sleep disorders in haemodialysis patients [8–10], since a substantial reduction of symptoms occurs after renal transplantation [11] or nocturnal dialysis [12].

It is well known that regardless of their sleep status, haemodialysis patients have limited functional capacity [13] and experience increased fatigability [14], exercise intolerance [15], muscle wasting and weakness [16], all factors shown to be important determinants of the QoL [17]. It is noteworthy that the fatigue symptoms induced by either the lack of restorative sleep or by the haemodialysis treatment share a common dominator; low day-time functionality and exercise intolerance.

Many studies dealing with haemodialysis fatigue have used various interventions, including exercise training, to improve functionality and to reverse muscle wasting and weakness as a means of improving the quality of haemodialysis patients' life [18,19]. Even though exercise capacity and QoL-related parameters do improve after the various interventions, dialysis patients do not approach the predicted age-adjusted fitness' levels and still remain functionally compromised compared to a sedentary healthy age-matched person [19]. It seems that so far, not all contributors to the well-known muscle weakness and exercise intolerance observed in haemodialysis and end-stage renal failure patients have been unmasked.

The aim of the present study was to investigate whether haemodialysis patients with OSAHS are subject to functional impairments of a larger magnitude compared to non-apneic haemodialysis patients as the result of disturbed restorative sleep. We hypothesized, that dialysis patients with OSAHS will have lower functional capacity and reduced QoL compared to dialysis patients with no such evidence.

Methods

Subjects

This cross-sectional study was undertaken between April 2005 and April 2007 in stable chronic dialysis patients who were dialysed at the University Hospital of Larissa, Greece. Forty-three haemodialysis patients were recruited from our dialysis unit and none of them received nocturnal dialysis (not an available modality). Entry criteria included being on chronic haemodialysis for 6 months or more with adequate dialysis delivery (KT/V >1.1). Patients were excluded if they had reasons for being in a catabolic state such as hyperthyroidism, active vasculitis, malignancies, HIV and opportunistic infections or inflammations that required intravenous antibiotics within 3 months prior to enrollment, since those conditions are known to affect muscle size, body composition and functionality. Ten haemodialysis patients were not eligible to participate in the study for various reasons [hyperthyroidism (4): refusal to participate (3), opportunistic infection (Staphylococcus Aureus) (3)]. The causes of renal failure in the participants were: diabetic nephropathy (5), glomerulonephritis (10), obstructive uropathy (2), vasculitis (2), polycystic kidneys (7), renovascular disease (5), hypertension (5), unknown reasons (7). None of our patients were alcoholic or consuming more than 5 units of alcohol per week. All patients gave informed consent for study participation. The study was approved by the Ethics Committee on Human Research at the University Hospital of Larissa, Greece.

Study design

Patients were studied on a weekly basis at the University Hospital of Larissa and affiliated clinics. They participated in an all-night in-hospital polysomnographic session for assessing the apnoea–hypopnoea index (AHI), followed the next morning by a CT, DEXA and a series of functional tests, before the dialysis session. All measurements were made in a blind fashion, since none of the investigators were aware of the AHI status of the patients. Routine monthly laboratory results were recorded for dialysis subjects. A single-pool Kt/V was calculated from pre- and post-dialysis BUN measurements using the Daugirdas II equation (http://www.tinkershop.net/nephro.htm) [20].

Body composition

Body composition measurements were made on a free dialysis day. Whole body, regional fat and lean body mass were measured by a dual energy X-ray absorptiometer (DEXA) system (Lunar model DPX Madison, WI). *Post hoc* regional analysis was performed as previously described [21].

The waist-to-hip ratio was calculated as waist circumference at the midway between the iliac crest and the lowermost margins of the ribs over the hip circumference at the maximum circumference of buttocks. An average of three readings of each measurement was taken for the calculation of the waist-to-hip ratio (WHR).

Visceral (VAT) and subcutaneous (SAT) adipose tissue of the abdominal areas at the level of L4-L5 lumbar area, was assessed by analysing images collected by a computed tomography (CT) system (Philips, Tomoscan SR5000) [22]. Muscle cross sectional area (CSA) and composition was assessed by images collected using the same CT set up. Six images of 2 cm apart were collected at the larger girth of the right thigh for each patient as described previously [23].

Image analysis of the CT slices was performed in a customized software program written in IDL (Interactive

Data Language Research Systems, Inc., Boulder, CO). This software, based on variations in signal intensity, allowed the quantification of visceral to subcutaneous adipose tissue (VAT/SAT), visceral to total adipose tissue (VAT/TAT) and the separate quantification of muscle (contractile), fat (non-contractile) and miscellaneous (connective tissue, fascia) components of the total cross-sectional area of the muscle compartment of the leg (excluding subcutaneous adipose tissue and bones) [24]. The CT slices with the largest cross-sectional area in the thigh were analysed for each subject. Each slice was measured three times and the average value was taken. Subcutaneous adipose tissue (SAT) of the thigh muscle was quantified as the area below the skin and above the muscle fascia on the same CT slice used to quantify muscle size and percentage of muscle content [24].

The ankle-to-brachial index (ABI) was calculated using an oscillometric method as described previously [25].

Functional capacity

General physical condition was assessed by using the North Staffordshire Royal Infirmary (NSRI) walk test [26]. Briefly the NSRI walk test consists of the following: the time in seconds taken to complete a task of 50 m continuously walking, climbing up 22 stairs (total elevation 3.3 m), climbing down 22 stairs and walking back 50 m to the starting point. Muscle functional capacity (muscular strength and endurance) was assessed using three objective measures as previously described: [13,27] (1) time to perform five sit to stand cycles (STS-5) representing the level of muscle power, (2) number of sit to stand cycles achieved in 60 s (STS-60) representing muscular endurance, (3) time to walk a distance of 6.06 m (20 ft) at normal pace (slow walk) and fast pace (fast walk) representing everyday functional capacity.

Nutritional status

The nutritional status of the patients was assessed using the 7-point subjective global assessment (SGA) scale. This method classifies the patients into seven categories (A, A–, B+, B, B–, C or C–) starting from well-nourished (A) to seriously malnourished (C–). The validity and reliability of this method of nutritional assessment has previously been reported in dialysis patients [28].

Polysomnography

Polysomnograms (Alice 4 computerized system Healthdyne, Marietta, GA) were collected overnight at the Sleep Disorders Laboratory of University General Hospital of Larissa as previously reported [29]. During the polysomnographic session the following parameters were recorded: electroencephalogram (C3/A2,C4/A1 and O1/A2); right and left electrooculogram; submental and tibial electromyogram; body position; electrocardiogram; thoracic and abdominal wall motion (piezoelectric transducers); oronasal airflow (three-pronged sensor); and oxygen saturation of haemoglobin (N-1000 oxymeter, Nellcor,Van Nuys, CA). Polysomnography was terminated upon final awakening. Sleep stages and arousals were determined using standard criteria [17,18]. Total sleep time was measured based on both the electroencephalogram and the laboratory technician's notes in case of a mismatch. Obstructive apnoea was defined as the presence of chest/abdominal wall motion in the absence of airflow for at least 10 s in duration. Hypopnoea was defined as: (1) a reduction in airflow signal amplitude of at least 50% compared to baseline; (2) the presence of chest/abdominal wall motion; and (3) oxygen desaturation of haemoglobin by 4% or with an arousal. The respiratory disturbance index (RDI) was equal to the sum of the number of hypopnoeas, obstructive and mixed apnoeas (apnoeas with both central and obstructive components), per hour of sleep. Sleep efficiency was calculated by dividing the total time asleep by the total time in bed after lights off. The arousal index was defined as the total number of arousals in sleep, divided by the total sleep time.

Sleep stages and arousals were determined using standard criteria [30,31]. The AHI was equal to the sum of the number of hypopnoeas, obstructive and mixed apnoeas (apnoeas with both central and obstructive components) per hour of sleep.

Questionnaires

QoL was assessed by using the SF36 QOL questionnaire adjusted and validated in dialysis patients [32]. The questionnaire materials were completed with the interview method by experienced personnel. The Epworth sleepiness scale [33] was used to assess daytime sleepiness by the interview method. The Zung self-rating depression scale [34] was used to assess levels of depression. This questionnaire is very sensitive to the early signs of depression and has been used successfully in haemodialysis patients [35]. Restless legs syndrome (RLS) symptoms were identified by using the RLSQ, a patient-completed instrument that has been shown to be a reliable screening tool for RLS [36]. Quality of sleep was estimated using a 7-day sleep diary adapted from the University of Massachusetts Medical School website (http://healthnet.umassmed.edu/mhealth/WeeklySleepQuestionnaire.pdf). The sleep diary contained questions about how often during the previous week dialysis patients experienced any of the following: (1) difficulties falling asleep, (2) number of nocturnal awakenings, (3) difficulties remaining asleep, (4) the sensation of waking-up tired and fatigued, (5) day time stress and (6) how often did they feel refreshed after the night's sleep. The sleep diary scored as: 'never' (0 points), '1–2 times a week' (1 point), '3–5 times a week' (2 points), '6–7 times a week' (3 points). For question number 6 the scoring was reversed with 3 points for the answer 'never', and 0 points for the answer '6–7 times a week'. The sleep diary score was calculated as the sum of the total points with the minimum at zero points and the maximum score at 18.

Statistical analysis

The primary aim of this study was to assess any differences in functional capacity (assessed by functional tests) between the two study groups. Secondary aims were to compare groups for any differences in muscle size, composition and visceral adiposity (assessed by CT scans) as well as whole-body composition (assessed by DEXA). Unpaired *t*-tests for continuous normally distributed variables; chi-square, for categorical variables; were used to compare groups. All variables were compared by using AGE, BMI and years in

Table 1. Patient characteristics, presented as pool data (both groups) and divided as low and high apnoea hypopnoea index score

Variables	Pool data	Spearman rank correlation to AHI	Low-AHI	High-AHI	*P*-values[a]
N	43	N/A	21	22	
Female/Male	13/30	N/A	9/12	4/18	0.21[b]
Age[a] (year) (range)	56.6 ± 19.4 (18–79)	$r = 0.369$, $P = 0.01$	47.9 ± 18.3 (18–75)	60.6 ± 13.5 (36–79)	**0.01**
BMI[a] (kg/m^2)	24.8 ± 4.1	$r = 0.315$, $P = 0.04$	23.5 ± 3.4	26.5 ± 4.3	**0.01**
KT/V	1.2 ± 0.4	$r = -0.423$, $P = 0.01$	1.2 ± 0.3	1.1 ± 0.5	0.20
Years in dialysis	2.1 ± 1.1	$r = 0.331$, $P = 0.03$	1.6 ± 1.1	2.4 ± 0.9	**0.01**
Smokers (*N*)	13 (30%)	N/A	6 (29%)	7 (32%)	0.60
SGA (A/B/C)	30/10/3	$r = -0.01$, $P = 0.92$	14/5/2	16/5/1	0.37
Diabetes prevalence	5 (12%)	N/A	2 (10%)	3 (14%)	0.37[b]
Hypertension prevalence	23 (53%)	N/A	11 (52%)	12 (54%)	0.26[b]
Cardiovascular disease	9 (21%)	N/A	4 (19%)	5 (23%)	0.21[b]
Ankle brachial index	1.2 ± 0.2	$r = 0.398$, $P = 0.02$	1.1 ± 0.1	1.2 ± 0.2	0.10
Body composition (DEXA)					
LBM (kg)	44.5 ± 8.5	$r = -0.001$, $P = 0.99$	43.3 ± 8.9	45.9 ± 8.9	0.12
Body Fat (%)	26.4 ± 12.8	$r = 0.185$, $P = 0.40$	26.4 ± 12.8	26.3 ± 13.4	0.91
Leg LBM (kg)	14.3 ± 3.3	$r = -0.210$, $P = 0.34$	14.4 ± 3.3	14.3 ± 3.4	0.91
WHR	1.0 ± 0.1	$r = 0.360$, $P = 0.04$	0.9 ± 0.1	1.0 ± 0.0	**0.01**
SF-36 Quality of Life					
Total score	66.2 ± 18.4	$r = -0.191$, $P = 0.24$	71.4 ± 16.9	63.8 ± 19.3	0.26
Physical function	63.6 ± 29.6	$r = -0.153$, $P = 0.35$	66.3 ± 33.3	62.5 ± 27.6	0.65
Vitality	69.9 ± 16.9	$r = -0.361$, $P = 0.03$	76.0 ± 15.9	64.5 ± 16.6	**0.05**
Mental health	71.2 ± 20.0	$r = -0.221$, $P = 0.18$	71.7 ± 19.6	62.9 ± 20.5	0.27

Data are mean ± SD. BMI, body mass index; LBM, lean body mass; WHR, waist to hip ratio; KT/V, dialysis efficiency; SGA, subjective global assessment. An unpaired *t*-test was used for assessing the differences between the two groups. Spearman rank correlation test was used to assess the relation between AHI and the examined variables.
[a]The comparison between the two groups were performed by using AGE, BMI and years in dialysis as covariates.
[b]For categorical data a chi-square test was performed.

dialysis as covariates. Spearman rank correlation test was used to assess the relation between AHI and the examined variables. To further adjust for any differences between the groups in age, a paired analysis was performed where patients matched by age (within 3 years), sex and BMI and groups were compared by using unpaired *t*-test analysis. Two-tailed *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using a commercially available statistical analysis software, Statview version 5.0.1 (SAS Institute Inc. Cary, NC). Reported data are mean ± SD.

Results

The patient demographic characteristics, dialysis compliance, body composition, nutritional status and QoL parameters are shown in Table 1. Briefly, 43 dialysis patients (13 F/30 M – 56.6 ± 19.4 years) underwent a polysomnographic examination to determine their AHI and they were divided in two groups according to their AHI score: the low-AHI group ($N = 21$, 9 F/12 M, AHI = 1.8 ± 1.3) and the high-AHI group ($N = 22$, 4 F/18 M, AHI = 28.8 ± 22.3) as shown in Tables 1 and 2.

Our patients received weekly doses of EPO as standard care (Hct 37 ± 2%). There were no gender differences between our groups however, age, BMI and years in dialysis were found to be statistically different and therefore all statistical analyses were adjusted statistically for those differences (as shown in Tables 1–4). Age correlated poorly with AHI ($r = 0.369$, $P = 0.01$) and moderately with muscle composition ($r = -0.558$, $P = 0.01$). No differences in KT/V were found between the two groups (Table 1). VAT correlated strongly with BMI ($r = 0.682$, $P = 0.001$) and moderately with functional capacity ($r = 0.558$, $P = 0.001$) and AHI ($r = 0.530$, $P = 0.001$).

The QoL score did not differ between the two groups. The majority of our patients were well nourished, with 66 and 73% of the low- and high-AHI patient groups, respectively belonging to the A score.

Polysomnographic assessment and quality of sleep

By definition, the low-AHI group had better sleep architecture and normal apnoea indices than the high-AHI group (Table 2). The restless legs syndrome (RLS) and the periodic limb movement disorder (PLMD) prevalence did not differ statistically between the two groups. Self-assessed depression (Zung DS), sleep diary and daily sleepiness (ESS) were found to be significantly different between the two groups. ESS correlated significantly but poorly with AHI ($r = 0.403$, $P = 0.02$).

Functional capacity

Patients with high AHI demonstrated significantly impaired muscle functional capacity in all but one test performed (the normal walk test) compared to patients with low AHI with (Table 3).

Body composition

Total body composition and *post hoc* regional analysis of the DEXA scans, did not reveal any statistically significant differences between the two groups. However, central adiposity was significantly different as indicated by both the WHR index (Table 1) and CT analysis (Table 4).

Specifically, analysis of the CT scans revealed that patients with high AHI had 23% larger abdominal areas, 61% increased visceral adiposity, 67% increased VAT/TAT ratio and 80% increased VAT/SAT ratio, indicating increased central adiposity (significant fat deposition in the visceral area—Table 4) compared to the low-AHI group. There was no gender effect in visceral adiposity indicating that both sexes were affected similarly (data not shown). VAT correlated strongly with BMI ($r=0.682$, $P=0.001$), functional capacity ($r=0.558$, $P=0.001$) and ESS ($r=0.414$, $P=0.05$). BMI correlated strongly with percent body fat ($r=0.780$, $P=0.001$) but not with LBM ($r=-0.289$, $P=0.19$).

Although thigh muscle CSA did not differ statistically between the two groups, the extramyocellular lipids deposition (EMCL, fat deposited between muscle fibres) in the muscle was found to be significantly increased by 27% in the high-AHI group compared to the low-AHI group (Table 4). Subcutaneous fat deposition at the thigh area did not differ statistically between the two groups (Table 4).

Table 2. Polysomnographic evidences for obstructive sleep apnoea–hypopnoea syndrome

Variables	Low-AHI	High-AHI	*P*-values[a]
Polysomnography			
Sleep duration (min)	320.4 ± 86.8	257.2 ± 80.2	**0.01**
Apnea hypopnoea index	1.8 ± 1.3	28.8 ± 22.3	**0.01**
Central apnoea index	0.3 ± 0.3	0.8 ± 1.3	0.06
Obstructive apnoea index	0.0 ± 0.1	3.4 ± 6.5	**0.04**
Stage 1 (%TST)	9.3 ± 5.4	19.9 ± 13.8	**0.01**
Stage 2 (%TST)	52.6 ± 10.7	59.2 ± 15.3	0.10
Stage 3 (%TST)	9.3 ± 3.8	5.6 ± 6.5	**0.05**
Stage 4 (%TST)	9.6 ± 5.7	4.2 ± 9.4	**0.01**
REM (% TST)	17.9 ± 8.8	9.2 ± 8.4	**0.01**
Arousal index (events/hour)	11.0 ± 5.6	39.3 ± 20.3	**0.01**
% O_2 Saturation	95.3 ± 1.7	92.4 ± 2.2	**0.01**
Desaturation index (events/hour)	4.7 ± 5.7	37.9 ± 30.5	**0.01**
Isolated leg movement Index (events/hour)	17.5 ± 28.8	42.8 ± 72.9	0.11
PLMD index (events/hour)	1.9 ± 4.6	8.4 ± 21.5	0.29
Questionnaires			
Sleep diary	3.5 ± 3.0	8.3 ± 5.6	**0.01**
Epworth sleepiness scale	3.4 ± 2.6	5.4 ± 2.8	**0.01**
Zung depression scale	36.1 ± 7.9	42.9 ± 8.5	**0.01**
Restless legs syndrome	7/21	7/22	0.43

Data are mean ± SD; TST, total sleep time; REM, rapid eyes movement stage; isolated leg movement index, leg movements during total sleep time which do not meet the PLM criteria; PLMD, periodic leg movement disorder.
An unpaired *t*-test was used for assessing the differences between the two groups.
[a]All statistics were performed by using AGE, BMI and years in dialysis as covariates.

Age, sex and BMI-matched paired analysis

To further account for age and BMI differences, in addition to using AGE, BMI and years in dialysis as covariates in statistical analysis of all subject data, a separate paired analysis was performed after matching patients by age, sex and BMI ($N=10$/group). The remaining patients did not have counterparts in the other group of the same sex and BMI (within 1 unit) and within 3 years of age. The analysis results are listed in Table 5. The results from the matched paired analysis were in agreement with the statistically adjusted analysis of the entire study cohort for all of the parameters tested.

Discussion

Patients with a high AHI were found to have reduced functional capacity, diminished physical performance, altered muscle composition favouring fat deposition and increased visceral adiposity compared to dialysis patients without the syndrome. Based on this evidence, it appears that OSAHS is concurrent with further exercise intolerance and poorer functional capacity in patients receiving haemodialysis therapy.

It is evident now that sleep disorders affect a large proportion of renal failure patients [37]. In our study,

Table 3. Functional capacity score presented as pool data (both groups) and divided as low and high apnoea hypopnoea index score

Variables	Pool data	Spearman rank correlation with AHI	Low-AHI	High-AHI	*P*-values[a]
Normal walk (s)	6.4 ± 1.7	$r=0.297$, $P=0.05$	5.9 ± 1.8	6.5 ± 1.4	0.22
Fast walk (s)	4.2 ± 1.3	$r=0.335$, $P=0.03$	3.7 ± 1.0	4.6 ± 1.3	**0.01**
Sit to stand 5 reps (s)	10.8 ± 3.8	$r=0.464$, $P=0.01$	9.2 ± 3.5	12.2 ± 3.6	**0.01**
Sit to stand 30 s (reps)	15.2 ± 4.9	$r=-0.487$, $P=0.01$	17.5 ± 5.6	13.2 ± 4.9	**0.01**
Sit to stand 60 s (reps)	29.3 ± 9.7	$r=-0.537$, $P=0.01$	34.2 ± 10.8	24.8 ± 5.6	**0.01**
NSRI walk test (s)	90.1 ± 36.7	$r=0.385$, $P=0.01$	73.5 ± 30.4	105.0 ± 36.8	**0.01**

Data are mean ± SD.
An unpaired *t*-test was used for assessing the differences between the two groups. Spearman rank correlation test was used to assess the relation between AHI and the examined variables.
[a]Comparisons between the two groups were performed by using AGE, BMI and years in dialysis as covariates.

Table 4. Abdominal and muscle CT image analysis presented as pool data (both groups) and divided as low- and high-apnoea hypopnoea index score

Variables	Pool data	Spearman rank correlation with AHI	Low-AHI	High-AHI	*P*-values[a]
Visceral and subcutaneous adiposity					
Abdominal CSA (cm^2)	605.1 ± 63.1	$r = 0.458$, $P = 0.02$	545.5 ± 130.3	671.6 ± 165.2	**0.01**
% VAT	55.3 ± 21.5	$r = 0.576$, $P = 0.01$	41.8 ± 20.0	67.5 ± 16.1	**0.01**
VAT/TAT	0.4 ± 0.2	$r = 0.440$, $P = 0.01$	0.3 ± 0.1	0.5 ± 0.1	**0.01**
VAT/SAT	0.7 ± 0.4	$r = 0.316$, $P = 0.11$	0.5 ± 0.3	0.9 ± 0.4	**0.01**
Thigh muscle composition					
Muscle CSA (cm^2)	97.0 ± 26.5	$r = 0.09$, $P = 0.64$	94.5 ± 23.4	102.3 ± 27.6	0.32
EMCL CSA (cm^2)	20.3 ± 5.1	$r = 0.430$, $P = 0.03$	17.7 ± 5.6	22.4 ± 3.7	**0.01**
SAT (cm^2)	131.0 ± 61.6	$r = -0.06$, $P = 0.63$	142.4 ± 57.0	125.6 ± 66.3	0.24

Data are mean ± SD. CSA, cross-sectional area; VAT, visceral adipose tissue; TAT, total adipose tissue; SAT, subcutaneous adipose tissue; EMCL, extramyocellular lipids.
An unpaired *t*-test was used for assessing the differences between the two groups. Spearman rank correlation test was used to assess the relation between AHI and the examined variables.
[a]All statistics were performed by using AGE, BMI and years in dialysis as covariates.

Table 5. Age, sex and BMI matched paired analysis

Age, sex and BMI Matched analysis	Low-AHI $N = 10$	High-AHI $N = 10$	*P*-values
Age (years)	55.9 ± 12.6	56.0 ± 10.9	0.98
Sex (F/M)	5/5	5/5	N/A
AHI	1.8 ± 1.4	29.4 ± 22.5	**0.01**
Years in dialysis	1.2 ± 0.9	2.1 ± 0.8	**0.03**
BMI	24.4 ± 2.9	25.1 ± 3.3	0.53
KT/V	1.3 ± 0.3	1.3 ± 0.7	0.89
LBM (kg)	41.0 ± 10.1	41.1 ± 5.3	0.94
VAT/TAT	0.3 ± 0.1	0.6 ± 0.2	**0.01**
Muscle CSA (cm^2)	95.7 ± 30.6	91.0 ± 22.4	0.76
EMCL CSA (cm^2)	17.1 ± 4.1	22.3 ± 3.3	**0.04**
Fast walk (s)	3.7 ± 0.9	5.0 ± 1.3	**0.01**
Sit to stand 60 s (reps)	33.9 ± 8.8	24.6 ± 3.3	**0.01**
NSRI walk test (s)	78.2 ± 29.5	105.1 ± 34.6	**0.05**
SF36 QoL	74.5 ± 14.7	64.8 ± 19.0	0.27

Data are mean ± SD. AHI, apnea hypoxia index; BMI, body mass index; VAT/TAT, visceral adipose tissue to total adipose tissue; CSA, cross sectional area; EMCL, extramyocellular lipids (fat infiltration); NSRI, north Staffordshire royal infirmary test; SF36 QoL, short form 36 quality of life.
An unpaired *t*-test was used for assessing the differences between the two matched subgroups.

51% of our patients examined were found to suffer from OSAHS. Similar data using similar methodology have been published in non-dialysed patients (54–65%) [38] implying that those disorders could possibly be carried over from the pre-dialysis stage. Studies assessing sleep quality using self-assessment surveys and questionnaires have found a wider range of sleep disorders prevalence varying between 20 and 80% in haemodialysis [39] and peritoneal dialysis [40] patients. Nevertheless, it appears that dialysis patients may have one extra reason to feel weak [14] and unable to perform daily activities [13]. Sleep deprivation in an otherwise healthy population exerts a negative effect in the QoL [41,42], in the recovery from fatigue [43], in general health and in life expectancy [44]. Even a modest sleep restriction, of 2 weeks duration, can exert a significant effect in daily sleepiness, mood and activity [45]. It is expected therefore that chronic exposure to insufficient amounts and quality of sleep can induce a wide range of psycho-physiological alterations on the human body [46] not dissimilar to those symptoms commonly observed in haemodialysis patients [47]. Since the majority of dialysis patients suffer from OSAHS and other sleep disorders, it is conceivable to assume that a percentage of the diminished exercise capacity and reduced QoL could be attributed to the chronic lack of sufficient and continuous sleep. Indeed, in our study the arousal index of the high-AHI patients was increased by 4-fold compared to the low-AHI patients (Table 2) making it almost impossible for the high-AHI patients to get an undisturbed and restorative night's sleep. It seems therefore that the chronic lack of good sleep could contribute to the observed 43% decrease in general endurance and to the 27% decreased muscle strength in the high-AHI patients compared to the low-AHI patients (Table 3). To our knowledge this is the first study to indicate that a chronic reduction of sleep quality and quantity, related to OSAHS, could play a role in the magnitude of the impairment of functional capacity in haemodialysis patients.

Our data showed that the reduction in functional capacity was accompanied by changes in muscle composition, favouring fat infiltration in the thigh muscles in those patients with high AHI in both adjusted and matched analysis. We have previously shown that fat infiltration along with muscle atrophy are the most prominent characteristics of patients receiving dialysis therapy [13,24]. Likewise in a non-renal failure population, inactivity has been linked to increased fat deposition in the skeletal muscles of lean and obese individuals [48]. Therefore it is conceivable to deduce that a reduction in sleep quality can lead to an increased sensation of fatigue, which in turn may lead to a further reduction in physical activity, a sequence that in time could lead to compounded muscle atrophy and increased fat infiltration [13].

Indeed, the vitality scale assessed through the SF36 questionnaire was different between the two groups and correlated significantly with AHI (Table 1) implying that patients with sleep disturbances are more likely to experience fatigue throughout the day. Although we do not have direct measurements of daily activity, the results from the functional assessment closely follow the 'reduced physical activity' profile we have previously published using 3D accelerometers [13,24]. Still, looking at a limited ($N = 20$, Table 5) age, sex and BMI paired analysis we found that the excess of fat infiltration in the high-AHI group is not due to the increased age but possibly due to OSAHS prevalence.

Interestingly, thigh muscle CSA did not differ between the two groups with both statistical approaches, even though we expected that the high-AHI group would demonstrate reduced muscle size in line with the reduced functional capacity. In fact, the high-AHI group muscle size values were similar to those found in the low-AHI group and other dialysis studies published in the past [24]. It seems that in our case, factors that affect muscle composition and functionality do not affect muscle size at the same magnitude. Further studies need to fully unmask the true contributors of muscle size and increased fat infiltration in the skeletal muscles of apneic haemodialysis patients.

It is known that dialysis patients have higher levels of visceral adipose tissue at any BMI level compared to healthy individuals [49], an observation that is also supported by our data. Visceral fat is strongly related to the level of physical activity [50] and it has been linked with the OSAHS in a fashion that implicates insulin resistance and hypercytokinemia [51]. In agreement with others, in our study, the visceral adiposity correlated strongly with functional capacity and AHI. Indeed, in both adjusted and paired analysis, patients with high AHI demonstrated a 61% higher visceral adiposity and a 43% lower physical functionality compared to non-apneic patients. It is possible however, that the increased visceral adiposity, and altered muscle composition could be the causes of sleep disorders and not vice versa. In order to assess whether and to what extent fat deposition in central areas and muscles was implicated and/or responsible for our observations, further studies are needed.

Notably, the observed differences in VAT between apneic and non-apneic patients were not followed by significant differences in LBM and total body fat. It is known that patients with sleep apnoea are often obese [52] but in our study, total body composition did not stand out as a difference. Rather, it was an altered fat distribution that characterized patients with high AHI. Differences in fat distribution between our groups were not due to the nutritional status of our patients since both groups were found to be equally nourished.

Against our original hypothesis, the total score from QoL questionnaire did not differ between the two sleep apnoea groups even though apneic patients scored higher in the Zung depression scale ($P = 0.01$) compared to non-apneic patients. It is possible that any separate effects of sleep disturbances on QoL, are masked by the profound effects of renal disease in the QoL [53].

Some other limitations in this cross-sectional study need to be discussed, mainly the age difference between the two groups. Even though we performed our statistics with age, BMI and years in dialysis as covariates (Tables 1–4), we still recognize the potential bias we might have imposed to our study. To further explore the age differences, we performed an age, sex and BMI-matched pair analysis for the main variables discussed in this paper (Table 5). This analysis revealed that OSAHS is still implicated in the reduced functional capacity found in haemodialysis patients.

In conclusion, we have shown for the first time that, compared to their non-apneic counterparts, haemodialysis patients with OSAHS are weaker, with a further reduced functional capacity, increased visceral adiposity and altered muscle composition favouring fat infiltration. The mechanisms by which OSAHS might affect functionality and body composition are not understood nor were they investigated by us. It is possible that the effects of sleep of a reduced quality and quantity on the global health of dialysis patients could speed up the deterioration of functional capacity that these patients experience. Our study indicates that the prevalence of sleep disorders should be accounted for in the assessment of the efficacy of rehabilitation interventions in renal patients, as it might contribute to the variations in subject responsiveness reported in the literature. Our results also point to two research directions that should be investigated. First, it should be examined whether any interventions to improve OSAHS symptoms in these patients would also improve their overall functional capacity. On the reverse, it should be investigated whether interventions designed to improve muscle composition and functionality in dialysis patients might in parallel improve the quality of sleep in those patients that concurrently suffer from sleep disorders.

Acknowledgements. This study has been supported by the Greek Scholarship Foundation (IKY) and by the 03ED375 research project, implemented within the framework of the 'Reinforcement Programme of Human Research Manpower' (PENED) and co-financed by National and Community Funds (25% from the Greek Ministry of Development-General Secretariat of Research and Technology and 75% from E.U.-European Social Fund). We would like to thank Dr Zigoulis and Dr Efeoglou for their help at the sleep laboratory, Mrs Katsogridaki for help with the nutritional assessment, Mrs Oustampasidou (head nurse) and the nursing staff at the haemodialysis unit of the University Hospital of Larissa for their cooperation, and all haemodialysis patients for participating in this study.

Conflict of interest statement. None declared.

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Received for publication: 28.1.07
Accepted in revised form: 24.7.07