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The Relationship Between Orexin-A Levels, Nutritional Status and Quality of Sleep in Hemodialysis Patients

[Hemodiyaliz Hastalarında Orexin-A Düzeyleri, Nutrisyonel Durum ve Uyku Kalitesi Arasındaki İlişki]

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ABSTRACT

Objective: Symptoms such as anorexia and sleep disturbances are common and cause a significant reduction in quality of life in hemodialysis patients. Orexin-A, which is a neuropeptide produced in lateral hypothalamic neurons and involved in regulation of feeding behavior, energy metabolism and sleep-wake cycle, is a good candidate to play a role in sleep and feeding disturbances in these patients. The aim of this study was to investigate the relationship between orexin-A levels and anorexia and sleep disturbances in hemodialysis patients.

Subjects and Methods: 70 hemodialysis patients and 70 age and sex matched healthy controls were compared according to their orexin-A levels. Plasma orexin-A levels were measured with the Enzyme Immunassay method. The Subjective Global Assessment Scale to assess nutritional status, and Pittsburg Sleep Quality Index to assess quality of sleep were used.

Results: The mean orexin-A level of the patients was significantly lower than controls ($p<0.001$). Body mass index ($r=-.313$, $p=0.01$) and parathormone ($r=-.341$, $p=0.006$) were significantly correlated with orexin-A levels. After multivariate linear regression, the significance remained for body mass index ($p=0.01$) and triglyceride levels ($p= 0.03$).

Conclusion: These preliminary results may suggest that plasma orexin-A levels can be used as a biochemical marker for assessment of the nutritional state in hemodialysis patients.

Key Words: orexin-A, hemodialysis, malnutrition, sleep.

ÖZET

Amaç: Hemodiyaliz hastalarında anoreksi ve uyku bozukluğu gibi semptomlar yaygındır ve yaşam kalitesinde azalmaya neden olur. Oreksin-A, lateral hipotalamik nöronlarda üretilen bir nöropeptittir ve yeme davranışı, enerji metabolizması ve uyku-uyanıklık siklusunun düzenlenmesinde rol alır. Oreksin-A, hemodiyaliz hastalarında görülen yeme ve uyku bozukluğunda rol oynuyor olabilir. Bu çalışmanın amacı hemodiyaliz hastalarında serum oreksin-A düzeyleri ile anoreksi ve uyku bozukluğu arasındaki ilişkiyi araştırmaktır.

Gereç ve yöntem: Çalışmamızda 70 hemodiyaliz hastası ile 70, yaş ve cinsiyet açısından uyumlu sağlıklı bireyin oreksin-A düzeyleri karşılaştırıldı. Plazma oreksin-A düzeyleri enzim immünoassay yöntemi ile analiz edildi. Hastaların nutrisyonel durumunu değerlendirmek için "The Subjective Global Assessment Scale" ve uyku kalitesini değerlendirmek için "Pittsburg Sleep Quality Index" kullanıldı.

Bulgular: Hastaların oreksin-A düzeyleri kontrol grubun düzeylerinden anlamlı derecede daha düşüktü ($p<0.001$). Vücut kütle indeksi ($r=-.313$, $p=0.01$) ve parathormon ($r=-.341$, $p=0.006$) değerleri, oreksin-A düzeyleri ile anlamlı derecede korele idi. Multivariate lineer regresyon sonrası vücut kitle indeksi ($p=0.01$) ve trigliserit düzeyleri ($p= 0.03$) için anlamlı fark devam etti.

Sonuç: Bu ön çalışma sonuçları, plazma orexin-A düzeylerinin hemodiyaliz hastalarında nutrisyonel durumun değerlendirilmesi için biyokimyasal bir belirteç olarak kullanılabileceğini göstermektedir.

Anahtar Kelimeler: oreksin-A, hemodiyaliz, malnutrisyon, uyku.

Introduction

Patients with end stage renal disease (ESRD) experience numerous physical and emotional symptoms, which are serious in terms of medical outcomes and cause a decrease in functioning and well-being (1). A systematic review of symptoms that may cause a reduction in quality of life in ESRD has revealed that anorexia (25%-61%) and sleep disturbances (20%-83%) were among the most common (2).

Possible reasons for these symptoms in ESRD have been the focus of most clinical research during the last two decades. It has been proposed that uremic toxins, altered amino-acid patterns, leptin, ghrelin, neuropeptid Y and proinflammatory cytokines (such as tumor necrosis factor-α, interleukin-6) are involved in anorexia in hemodialysis (HD) patients which contributes to the development of malnutrition and cachexia (3-7). Sleep disorders were found to be common in HD patients and have been related to depression, gender, hemoglobin levels, advanced age and dialysis shifts in the morning (8-10). These findings suggest that pathogenesis of these symptoms is multi-factorial. The search for a common factor that would contribute to sleep and feeding related problems in hemodialysis patients is the main purpose of this study. We thought that the candidate molecule that might fulfill this purpose was orexin.

The neuropeptides orexin-A and B (also known as hypocretin 1 and hypocretin 2) are produced in lateral hypothalamic neurons and are involved in regulation of feeding behavior, energy metabolism and sleep-wake cycles (11). Orexins were initially identified as endogenous ligands for two orphan G-protein-coupled receptors (12). Their relation to feeding behavior was proved by the observation that intracerebroventricular injection of orexins during the light period induced feeding behavior in rats and mice (13). Subsequently, the finding that an orexin deficiency causes narcolepsy in humans and animals, has indicated that orexins may also have a crucial role in regulating sleep and wakefulness (14-15).

There are reasons to think that orexin may play a role in sleep and feeding disturbances in ESRD. First it was shown that prepro-orexin mRNA was detected in the kidneys (16). Secondly, orexin-A like immunoreactivity, was present in the urine obtained from healthy males (17). These findings suggest that in addition to the lateral hypothalamus, orexin-A is also produced by renal tubular cells and secreted into the urine.

In this study, we aimed to examine the relationship between plasma orexin-A levels and sleep and nutritional status in HD patients. Our hypotheses were; 1) Since it was previously shown that orexin-A may be produced by renal tubular cells (16,17), plasma orexin-A levels would be different between HD patients and healthy controls, 2) Plasma orexin-A levels would show some significant correlations with sleep and feeding disturbances in HD patients, since orexin-A has been shown to be involved in regulation of sleep and feeding behavior in humans and animals (13-15).

Materials and Methods

Setting

This prospective and controlled study was conducted by a collaboration of the Nephrology, Psychiatry and Medical Biochemistry Departments of Gazi University, Faculty of Medicine and was ethically approved by a local ethics committee (date: 21st April, 2008, number: 150).

Sample

There were two groups in this study. The first group consisted of patients who regularly received HD treatment for ESRD at Hemodialysis Clinic of the Nephrology Department. This unit has 90 patients, most of whom are treated twice or three times weekly in an HD program. The second group included age and sex matched healthy controls. All subjects participating in the study, signed a written consent form prior to the study.

Exclusion criteria for patients were: Being illiterate, being younger than 18 or older than 85 years old, having a cognitive impairment or mental retardation which would cause severe difficulty in filling out the self-rating scales, receiving a renal replacement therapy other than HD (such as peritoneal dialysis or renal transplantation), and not giving informed consent. 75 patients fulfilled the criteria and among them, 70 finished the study. Duration of chronic renal failure and HD treatment were recorded by researchers. Body mass index (BMI) was calculated and albumin, triglyceride and total cholesterol levels measured for nutritional status (18,19). Blood samples for orexin-A levels were obtained. Parathormone (PTH) levels evaluated for energy metabolism (11). The Subjective Global Assessment Scale was completed by a nephrology fellow (R.M.). Patients filled out the Pittsburg Sleep Quality Index.

Exclusion criteria for the age, sex and education matched control group were: Having malnutrition (according to BMI), having a diagnosed renal illness and/or having a diagnosed medical illness, which would cause a vulnerability to renal failure (such as diabetes mellitus, hypertension, or autoimmune illness). Height and weight of controls were recorded and BMI was calculated.

Venous blood samples for orexin-A levels and all other parameters were obtained from fasting subjects at the same time (8.00 a.m.), before HD sessions. *Blood* samples were collected into the *EDTA and aprotinin* containing tubes. *Then plasma* was immediately separated by *centrifugation at 1600xg at 4ºC for 15 minutes*. Plasma samples were kept at -80*ºC until analysis.*

Instruments

Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is a self-

rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval (20). It has seven sub-scales, namely: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

The sum of scores for these seven components yields one global score. In the original article, clinical and psychometric properties of the PSQI were supported using data collected from 52 "good" sleepers (52 healthy subjects) and "poor" sleepers (54 depressed patients and 62 patients with sleep disorders). In a study conducted to characterize the relationships between PSQI and Epworth Sleepiness Scale (ESS), it was found that the PSQI is more closely related to psychological symptom ratings and sleep diary measures than the ESS (21). For this study, a Turkish translation version of PSQI was used (22).

Subjective Global Assessment (SGA)

The Subjective Global Assessment (SGA) is a tool used by care providers to assess nutritional status and aid in prediction of nutritionally-associated clinical outcomes. Although it was first used as an assessment tool for nutritional status in preoperative surgical patients and to predict postoperative infections (23), it has been widely used in many clinical settings since then. The SGA has been recommended by the National Kidney Foundation (NKF) Kidney Disease/Dialysis Outcomes and Quality Initiative (K/DOQI) for use in nutritional assessment in the adult dialysis population (24). It has been shown that the 7-point scale SGA (also used in the present study) is a reliable and valid tool for nutritional assessment in adults on HD (25). The assessment is based on the patient's history in the preceding 6 months (gastrointestinal symptoms such as anorexia, nausea, vomiting, diarrhea, dietary food intake, as well as functional capacity and comorbidities) and physical examination (loss of subcutaneous fat over the triceps and mid-axillary line of the lateral chest wall, muscle wasting in the deltoids and quadriceps). Each component is rated on a scale of 1 to 7 with a possible total range from 7 to 35. A value of 7 is normal, while 35 indicates the severe malnutrition. For this study, the patients were classified in terms of three major SGA scores: very mild risk to well-nourished (1 or 2 points from most categories or significant, continued improvement), moderate malnutrition (3, 4 or 5 points from most categories, no clear sign of normal status or severe malnutrition) and severe malnutrition (6 and 7 points in most categories/significant physical signs of malnutrition).

Laboratory Methods:

Plasma orexin-A levels were measured with the EIA (Enzyme Immunassay) method using a commercial kit (Phoenix Pharmaceuticals Inc., Burlingame, USA) with a microplate ELISA reader (BIO-TEK, ELx800). Minimum detectable concentration was 0.22 ng/mL. Intra-assay and inter-assay variation coefficients were <5% and <14%, respectively. Serum parathormone (PTH), total cholesterol, triglyceride and albumin levels for energy metabolism (11) were measured by autoanalyser (Abbott-Architect / ci16200 integrated platforms) using commercial kits (Abbott).

Statistical analysis

Statistical analysis of all data obtained was made by using the SPSS 10.0 version. *Chi-square* test was used to compare the two groups with regards to socio-demographic variables. The two groups were compared by using a Student's *t-test for independent samples* according to their age, height, weight, body mass index and orexin-A levels. *Pearson Correlations* were used for analyzing correlations between patients' orexin-A levels, PSQI and SGA scores, and parameters obtained from blood samples. Exploratory analyses, including variables which were thought to have statistically significant effect on orexin-A levels, were performed by using *multivariate linear regression* analysis with enter modeling. Analysis of covariance (ANCOVA) was used to compare the orexin-A levels among two groups that control the influence of covariates. A p value < 0.05 was considered statistically significant.

Results

Demografic characteristics of the patients and controls were presented in the Table 1. Mean orexin-A levels of the patients were significantly lower than controls (13.95±7.39 vs 20.39±8.96 respectively, p<0.001) (Figure 1). The BMIs of the controls were significantly higher than the patients (27.72±5.11 vs 23.15±4.27 respectively, p<0.001) (Table 1). Since a significant difference with regard to BMI was found between patient and control groups, analysis of covariance (ANCOVA) was performed in order to find if the orexin level difference was caused by the significant difference of BMI between these groups. Orexin-A levels were significantly different between the two groups in the ANCOVA model, where BMI was included as the covariance variable.

The patients' mean score from the SGA was 12.72±6.18 (7.00-35.00), and from the PSQI was 14.73±6.49 (0.00-27.00). Triglyceride, albumin and PTH levels were 184.72±119.60 mg/dL, 4.15±0.39 g/dL and 440.62±483.62 pg/mL, respectively.

Results of a Pearsons Correlation between orexin-A levels and age, some clinical features, blood sample results, scores of PSQI and SGA are shown in Table 2. There was a significant negative correlation between orexin-A levels and BMI (r=-.313, p=0.01) and PTH levels (r= -.341, p=0.006). However the correlations were weak.

Parameters that show nutritional status (triglyceride, albumin, BMI), PTH levels (since it was found to be correlated with orexin-A in Pearsons Correlation Analysis)

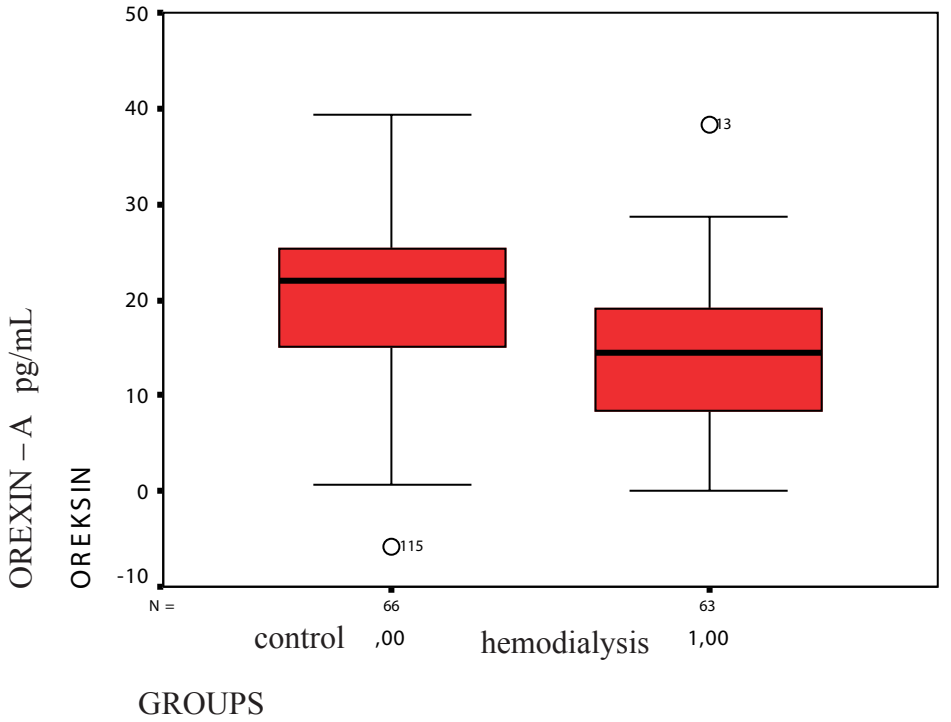

Figure 1. Plasma orexin-A levels (**control**: 20.39 ± 8.96, median: 22.07, **IQR**: 10.59; **hemodialysis**: 13.95 ± 7.39, median: 14.54, **IQR:** 11.03)

Table 1. Comparison of demographic and clinical features of patients and controls

	Patients	**Controls**	**P**
Gender; N (%)			
Female	25 (35.7)	28 (40.0)	0.6
Male	45 (64.3)	42 (60.0)	
Age (mean ± SD)	49.24 ± 15.95	48.89 ± 13.55	0.8
Chronic renal failure duration; months (min-max)	71.86±59.36 (2-300)	-	
Hemodialysis duration; months (min-max)	59.47±49.35 (1-216)	-	
BMI (mean ± SD)	23.15 ± 4.27	27.72 ± 5.11	<0.001*

BMI: Body Mass Index

Table 2. Pearsons Correlation Coefficients of serum Orexin-A levels of patients with different parameters

Variables	Serum Orexin-A levels of patients	P
Age	.020	0.8
Chronic renal failure duration (months)	.185	0.1
Hemodialysis duration (months)	.105	0.4
Body mass index	-.313	0.01*
PTH	-.341	0.006*
Total cholesterol	-.240	0.05
Triglyceride	-.210	0.09
Albumin	-.215	0.09
SGA	.187	0.1
PSQI	.189	0.1

SGA: Subjective Global Assessment, PTH: Parathormone, PSQI: Pittsburg Sleep Quality Index

Table 3. A multivariate linear regression model for the relationship between Orexin-A levels and variables which show nutritional status, sleep quality, PTH levels

(Constant: 23.866; r^2= 0.257)	Coefficients, B (P)	95% CI (Lower- Upper)
BMI (normal/ high)	-.36 (0.01)*	-9.433, -1.316
Triglyceride (normal/ high)	-.29 (0.03)*	-8.863, -0.407
Albumin (normal/ low)	.00 (0.99)	-.4156, 4.202
PTH (normal/ high)	.08 (0.51)	-5.063, 9.972
SGA (moderate-severe/normal-mild)	-.06 (0.62)	-7.621, 4.629
PSQI (good sleepers/poor sleepers)	.14 (0.30)	-1.939, 6.132

BMI: Body Mass Index, PTH: Parathormone, SGA: Subjective Global Assessment, PSQI: Pittsburgh Sleep Quality Index, CI: Confidence Interval

*: significant for $p<0.05$

and scores of PSQI and SGA, were analyzed in a model of multivariate linear regression. For this analysis, variables were classified as follows: BMI normal (<24) / high(>=24), PTH normal (10-65 pg/mL)/ high, triglyceride normal (50-200 mg/dL)/ high, albumin normal (4-5 g/dL)/ low, SGA moderate-severe malnutrition (>=21)/ mild malnutrition-normal (<21) and PSQI good sleepers (<15)/ poor sleepers (>=15) (the mean score was used for PSQI since the number of patients scoring below 5 was only three). Results are shown in Table 3.

BMI (95% CI= -9.433- -1.316, p=0.01) and triglyceride levels (95% CI= -8.863- -0.407, p=0.03) were the significant variables.

Discussion

Our first hypothesis was that orexin-A could be produced by renal tubular cells and plasma orexin-A levels would be different between HD patients and healthy controls, in which the results of our study was confirmed that HD patients' orexin-A levels were significantly lower than age and sex matched healthy controls. This result is contrary to the limited previous literature about orexin in chronic renal failure. Sugimoto et al. (26) were the first group to study the plasma orexin levels in patients on HD and they found an increased plasma orexin-A concentration in these patients. Li et al. (27), in their first study, explored the changes of orexin-A and neuropeptide Y in plasma and the hypothalami of rats with chronic renal failure and found that levels of orexin-A in the hypothalami were significantly lower but plasma levels were significantly higher in rats with chronic renal failure than in normal rats. In their second study (28), Li et al. found lower expression of prepro-orexin mRNA and orexin-receptor-1, and a higher expression of Ob-R in hypothalamus neurons of rats with chronic renal failure. All of these findings suggest that chronic renal failure may cause diminished clearance of orexin-A, but we found that orexin-A levels were indeed decreased in HD patients. There are some possible reasons for decrease in orexin-A levels in these patients. First, the previous finding that prepro-orexin mRNA is detected in markedly high levels in kidneys (16) and orexin-A like immunoreactivity is present in the urine obtained from healthy males (17); may suggest that in addition to the lateral hypothalamus, renal tubular cells may also synthesize orexin-A and secrete it into urine. Since renal function is decreased in chronic HD patients, synthesis of orexin-A by the kidneys may also be decreased. Secondly, orexin neural activity is under the influence of peripheral metabolic clues, such as leptin, which inhibits the activity of orexin neurons (29). Since chronic renal failure is associated with increased plasma levels of leptin, one may assume that leptin will inhibit orexin production in HD patients. But we do not know if this has caused the lower orexin-A levels in HD patients of our sample, since we did not evaluate the leptin levels of these patients. Evaluating hypothalamic secretion of orexin-A by using cerebrospinal fluid samples would be more suitable for testing such a suggestion.

Our second hypothesis was that plasma orexin-A levels would show some significant correlations with sleep and feeding disturbances in HD patients, was partly confirmed. We expected to find some significant correlation between orexin-A levels and sleep and nutritional disturbances in hemodialysis patients, but our results did not indicate that. There was no significant relationship between orexin-A levels and any kind of sleep-related disturbances evaluated by the PSQI. Rayner (30) has suggested that the reduced sleep time and increase in night time arousals, characteristic of the uremic sleep disorder, may be related to increased levels of orexin during the night, but to our knowledge, there is no clinical research to test this suggestion. We could not find a significant association between orexin-A levels and nutritional status of our patients as shown by SGA scores, either. Since this study is the first one to explore the relation of orexin-A levels with sleep and nutritional status of HD patients, we do not know if these results are replicable, and further studies are necessary to clarify this situation.

PTH levels showed a significant correlation with orexin-A levels, although this significance was not observed after multiple regression analysis. Yet, this finding that PTH levels are correlated with orexin-A levels in HD patients seems important, since PTH is one of the determinants of resting energy expenditure and inflammation in HD patients (31, 32). The finding that PTH was correlated with orexin-A levels, which is known to be involved in energy metabolism (11), may be another area of interest for future research.

The most important finding in this study was that orexin-A levels were significantly related to BMI. The International Society of Renal Nutrition and Metabolism has developed a new standard terminology for protein-energy wasting in chronic renal disease. Protein-energy wasting is diagnosed if three characteristics are present; 1) low serum albumin, transthyretin or cholesterol levels, 2) reduced body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy), 3) reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference) (33). It has been shown that hypertriglyceridemia (34), normal albumin levels (35) and being overweight (BMI=25-30) or obese (BMI>30) (36) are paradoxically associated with better survival (also called 'reverse epidemiology') in HD patients. For these reasons, we analyzed triglyceride, albumin levels and BMI, as well as SGA and PSQI scores into a multiple regression analysis. High triglyceride levels were found to be significantly associated with orexin-A levels. In addition, the significance continued for BMI even after multiple regression analysis. It has been well established that BMI is positively correlated with serum leptin levels. Since leptin has been shown to inhibit the activity of orexin neurons (29), this may have caused a significant reduction of orexin levels in patients with better nutritional status in this sample.

Conclusion

Of course one should be cautious when interpreting our results, since our results are preliminary because they are drawn from a small sample and only one center, and there is always a risk for multiple comparisons. Measuring leptin levels and another orexigenic hormones such as ghrelin levels in addition to orexin-A would lead to a better understanding of the significant findings of this study. Still, this study, being the first one to investigate the relationship between orexin-A and wake-sleep disturbances and nutritional status of HD patients, points out that plasma orexin-A levels may be used as a biochemical marker of the nutritional state in patients on hemodialysis; a finding which needs further support from future studies.

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References

[1] Curtin RB, Bultman DC, Thomas-Hawkins C, Walters BA, Schatell D. (2002) Hemodialysis patients' symptom experiences: effects on physical and mental functioning. Nephrol Nurs J 29: 567-574.

[2] Murtagh FE, Addington-Hall J, Higginson DJ. (2007) The prevalence of symptoms in end-stage renal disease: a systematic review. Adv Chronic Kidney Dis 14: 82-99.

[3] Wolf G, Chen S, Han DC, Ziyadeh FN. (2002) Leptin and renal disease. Am J Kidney Dis 39: 1-11.

[4] Bossola M, Tazza L, Giungi S, Luciani G. (2006) Anorexia in hemodialysis patients: an update. Kidney Int 70: 417-22.

[5] Muscaritoli M, Molfino A, Chiappini MG, Laviano A, Ammann T, Spinsanti P, Melchiorri D, Inui A, Alegiani F, Rossi Fanelli F. (2007) Anorexia in hemodialysis patients: the possible role of des-acyl ghrelin. Am J Nephrol 27: 360-5.

[6] Mak RH, Cheung W. (2007) Cachexia in chronic kidney disease: role of inflammation and neuropeptide signaling. Curr Opin Nephrol Hypertens 16: 27-31.

[7] Carrero JJ, Aguilera A, Stenvinkel P, Gil F, Selgas R, Lindholm B. (2008) Appetite disorders in uremia. J Ren Nutr 18: 107-113.

[8] Iliescu EA, Coo H, McMurray MH, Meers CL, Quinn MM, Singer MA, Hopman WM. (2003) Quality of sleep and health-related quality of life in haemodialysis patients. Nephrol Dial Transplant 18: 126-132.

[9] Merlino G, Piani A, Dolso P, Adorati M, Cancelli I, Valente M, Gigli GL. (2006) Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy. Nephrol Dial Transplant 21: 184-190.

[10] Pai MF, Hsu SP, Yang SY, Ho TI, Lai CF, Peng YS. (2007) Sleep disturbance in chronic hemodialysis patients: the impact of depression and anemia. Ren Fail 29: 673-7.

[11] Sakurai T. (2007) The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci 8: 171-181.

[12] Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yangisawa M. (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein coupled receptors that regulate feeding behavior. Cell 92: 573-585.

[13] Haynes AC, Chapman H, Taylor C, Moore GB, Cawthorne MA, Tadayyon M, Clapham JC, Arch JR: Anorectic, thermogenic and anti-obesity activity of a selective orexin-1 receptor antagonist in ob/ob mice. *Regul Pept* 2002; 104: 153-159.

[14] Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charney Y, Neslimolova S, Aldrich M, Reynolds D, Albin R, Li R, Hungs M, Pedrazzoli M, Padigaru M, Kucherlapati M, Fan J, Maki R, Lammers GJ, Nouras C, Kucherlapati R, Nishinos S, Mignot E. (2000) A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nature Med 9: 991-997.

[15] Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, Cornford M, Siegel JM. (2000) Reduced number of hypocretin neurons in human narcolepsy. Neuron 27: 469-474.

[16] Nakabayashi M, Suzuki T, Takahashi K, Totsune K, Muramatsu Y, Kaneko C, Date F, Takeyama J, Darnel AD, Moriya T, Sasano H. (2003) Orexin-A expression in human peripheral tissues. Mol Cell Endocrinol 205: 43-50.

[17] Takahashi K, Arihara Z, Suzuki T, Sone M, Kikuchi K, Sasano H, Murakami O, Totsune K. (2006) Expression of

orexin-A and orexin receptors in the kidney and the presence of orexin-A like immunoreactivity in human urine. Peptides 27: 871-877.

[18] Lowrie EG, Huang WH, Lew NL. (1995) Death risk predictors among peritoneal dialysis and hemodialysis patients: A preliminary comparison. Am J Kidney Dis 26: 220-228.

[19] Gamba G, Mejia JL, Saldivar S, Pena JC, Correa-Rotter R. (1993) Death risk in CAPD patients. The predictive value of the initial clinical and laboratory variables. Nephron 65: 23-27.

[20] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28: 193-213.

[21] Buysse DJ, Hall ML, Strollo PJ, Kamanck TW, Owens J, Lee L, Reis SE, Matthews KA. (2008) Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample. J Clin Sleep Med 4: 563-71.

[22] Agargun MY, Kara H, Anlar O. (1996) The validity and reliability of Pittsburgh Sleep Quality Index. Turk J Psychiatry 7: 107-115.

[23] Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. (1987) What is subjective global assessment of nutritional status? *J* Parenter Enteral Nutr 11: 8-13.

[24] K/DOQI, National Kidney Foundation: Clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* 2000; 35: S1-140.

[25] Kalantar-Zadeh K, Kleiner M, Dunne E, Lee GH, Luft FC. (1999) A modified quantitative subjective global assessment of nutrition for dialysis patients. Nephrol Dial Transplant 14: 1732-1738.

[26] Sugimoto T, Nagake Y, Sugimoto S, Ahagi S, Ichikawa H, Nakamura Y, Ogawa N, Makino H. (2002) Plasma orexin concentrations in patients on hemodialysis. Nephron 90: 379-383.

[27] Li JL, Zheng FL, Tan HB, Yin SY, Yang JH, Li Y, Bu YF. (2003) Orexin-A and neuropeptide Y levels in plasma and hypothalamus of rats with chronic renal failure. Zhonghua Yi Xue Za Zhi 83: 992-995.

[28] Li JL, Zheng FL, Tan HB, Li Y. (2004) Expression of orexin-A, orexin rceptor-1 and Ob-R of hypothalamus in rats with chronic renal failure. Zhonqquo Yi Xue Ke Xue Yuan Xue Bao 26: 56-61.

[29] Yamaka A, Beuckmann CT, Willie JT, Hara J, Tsujino N, Mieda M, Tominaga M, Yagami K, Sugiyama F, Goto K, Yanagisawa M, Sakurai T. (2003) Hypothalamic orexin neurons regulate arousal according to energy balance in mice. Neuron 38: 701-13.

[30] Rayner HC. (2003) Orexin as a possible cause of insomnia in dialysis patients. Am J Kidney Dis 41: 1335-1336.

[31] Utaha S, Avensani CM, Draibe SA, Kamimura MA, Andreoni L. (2005) Inflamation is associated with increased energy expenditure in patients with chronic kidney disease. Am J Clin Nutr 82: 801-5.

[32] Kamimura MA, Draibe SA, Avensani CM, Canziani ME, Colugnati FA, Cuppari L. (2007) Resting energy expenditure and its determinants in hemodialysis patients. Eur J Clin Nutr 61: 362-7.

[33] Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkol P, Treviao-becerra A, Wanner C. (2008) A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int 73: 391-398.

[34] Kilpatrick RD, McAllister CJ, Kouesdy CP, Derose SF, Kopple JD, Kalantar-Zadeh K. (2007) Association between serum lipids and survival in hemodialysis patients and impact of race. J Am Soc Nephrol 18: 293-303.

[35] Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn H, Kopple JD, Greenland S. (2005) Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. Nephrol Dial Transplant 20: 1880-1888.

[36] Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatirck RD, Horwich TB. (2005) Survival advantages of obesity in dialysis patients. Am J Clin Nutr 81: 543-554.