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Baseline serum leptin predicts peritoneal dialysis adequacy: a single-center prospective, longitudinal study

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Abstract. *Hyperleptinemia is often observed in peritoneal dialysis (PD) patients. But, there are few studies on the relationship between blood leptin level and PD survival, and, some of them contradict each other.*

The present study aimed to investigate the impact of PD initiation on the serum leptin concentrations and its association with PD adequacy.

Method. A total of 23 patients with end-stage renal disease (ESRD), who started the treatment with continuous ambulatory peritoneal dialysis (CAPD), were included in this prospective single-center observational longitudinal study. Among the patients, there were 15 men and 8 women; the average age of the patient population was 52.4 ± 12.3 years. The treatment with CAPD was performed using Dianeal PD 4 with glucose concentration of 1.36% and 2.27%. The patients were screened before PD initiation and after 3- and 12-month PD treatment. Leptin levels were determined in all patients using ELISA-method.

Results. The median serum leptin concentration at study entry was 10.6 [5.6-21.9] ng/mL. Leptin level and its dynamics during the year after PD treatment initiation were dependent on body mass index (BMI). The overweight or obese patients had ever-increasing leptin levels after 3- and 12- month PD treatment. Whereas in the PD patients with normal weight, we observed a significant decrease of leptin levels after 12-month PD treatment. Serum leptin concentration in the women was significantly higher compared with the men (46.4 [1.1-95] vs 9.8 [3.2-14.5] ng/mL; $p = 0.02$). Blood cholesterol levels had a positive correlation with serum leptin concentrations after 3- and 12- month PD treatment: $r = 0.53$, $p = 0.01$ and $r = 0.56$, $p = 0.008$, respectively. However, we did not find a statistically significant association of leptin with PD adequacy parameters after 3- and 12- month PD treatment of the patients.

In the Cox proportional hazard model adjusted for gender, serum leptin level demonstrated itself as the effective factor in PD adequacy survival: HR 5.3 (95% CI 1.7; 16.3).

PD adequacy survival was better in the patients with leptin concentrations above the median (≥10.6 ng/mL) compared with the patients who had serum leptin levels below the median (log rank test, $\chi 2 = 8.2$; $p = 0.0042$).

Conclusions. Our study have demonstrated markedly elevated serum leptin level in the overweight PD patients and its strong decrease during 12 months in the patients with normal weight. Low serum leptin level before PD initiation is associated with inadequate PD.

Key words: *peritoneal dialysis, serum leptin, adequacy.*

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Лептин сироватки як предиктор адекватності перитонеального діалізу: одноцентрове проспективне, поздовжнє дослідження

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Резюме. *Гіперлептинемія часто спостерігається у пацієнтів, які лікуються методом перитонеального діалізу (ПД). Проте, дослідження щодо взаємозв'язку між рівнем лептину крові і виживанням методу ПД є поодинокими та суперечливими.*

Дане дослідження спрямоване на вивчення впливу ініціації ПД на концентрацію лептину в сироватці крові та його зв'язку з адекватністю ПД.

Методи. Загалом 23 пацієнти з термінальною стадією хронічноїхвороби нирок, які почали лікування безперервним амбулаторним перитонеальним діалізом (ПАПД), були включені до проспективного одноцентрового обсерваційного поздовжнього дослідження. Серед пацієнтів було 15 чоловіків і 8 жінок; середній вік склав 52,4 ± 12,3 роки. Лікування ПАПД проводили з використанням Dianeal PD 4 з концентрацією глюкози 1,36% і 2,27%. Пацієнти були обстежені до початка ПД, через 3 і 12 місяців лікування. В усіх пацієнтів визначали рівень лептину методом ІФА.

Результати. Середній рівень концентрації лептину в сироватці крові до ініціації ПД становив 10,6 [5,6-21,9] нг/мл. Рівень лептину та його динаміка протягом року після початку лікування залежали від індексу маси тіла (ІМТ). У пацієнтів з надмірною вагою або ожирінням концентрація лептину збільшувалась як через 3 (p = 0.02) і 12 (p = 0.09) місяців лікування ПД. В той час як у пацієнтів з нормальною вагою ми спостерігали статистично значуще зниження рівня лептину після 12 місяців лікування (p = 0.003). Концентрація лептину сироватки у жінок була значно вищою у порівнянні з чоловіками (46,4 [1,1-95] проти 9,8 [3,2-14,5] нг/мл; p = 0,02). Рівні холестерину в крові мали позитивний кореляційний зв'язок з концентрацією лептину в сироватці крові через 3 і 12 місяців: r = 0,53, p = 0,01 і r = 0,56, p = 0,008, відповідно. Однак, ми не виявили статистично значущої асоціації лептину з параметрами адекватності ПД через 3 та 12 місяців лікування пацієнтів.

У пропорційній моделі ризику Кокса, скоригованої за статтю, рівень сироваткового лептину був ефективним фактором виживання адекватності ПД: HR 5.3 (95% ДІ 1.7; 16.3). Адекватність ПД була кращою у пацієнтів з концентрацією лептину вище медіани (≥ 10,6 нг/мл) порівняно з пацієнтами, у яких рівень сироваткового лептину був нижчим за медіану (логарифмічний тест, χ2 = 8,2; p = 0,0042).

Висновки. Наше дослідження демонструє підвищення рівня лептину сироватки у ПД пацієнтів з надлишковою масою тіла і його статистично значуще зниження протягом 12 місяців у пацієнтів з нормальною вагою. Низький рівень сироваткового лептину перед початком лікування асоційований з неадекватним ПД.

Ключові слова: *перитонеальний діаліз, лептин сироватки, адекватність.*

Introduction. Over the past years peritoneal dialysis (PD) has authenticated to be an effective method of renal replacement therapy (RRT) for end-stage renal disease (ESRD) patients [1]. But, despite the significant progress in technical survival, the duration of PD therapy is still limited [2, 3].

Leptin is a large molecular weight protein secreted by white adipocytes [4]. It regulates food intake and energy expenditure, and it also takes parts in the immune response, angiogenesis, and bone formation [4]. It has been suggested that the serum leptin concentrations are increased in obesity and associated with the fat content of the body [5]. Moreover, an elevation of the serum leptin level has been observed in chronic kidney disease (CKD), diabetes mellitus, coronary artery calcification, and arterial hypertension [4, 6-8]. The association of hyperleptinemia with glomerular mesangial cell hypertrophy, basement membrane thickening and reduced proximal tubule metabolic activity, resulting in albuminuria, and glomerular sclerosis have also been demonstrated [8].

Hypothetically, PD has several reasons for hyperleptinemia. First, the use of PD glucose-based fluids upregulates the metabolism of oxidative glucose in adipocytes and promotes the leptin production [9]. Second, a decrease in renal leptin clearance leads to high serum leptin level [10]. In addition, other conditions such as metabolic syndrome, malnutrition and chronic inflammation are positively associated with an increase in leptin levels in PD patients [11, 12]. Nevertheless, the dynamics of serum leptin concentration after PD initiation has not been characterized yet.

The present study aimed to investigate the impact of PD initiation on the serum leptin concentrations and its association with PD adequacy.

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Materials and methods. *Study Design and Subjects.* This prospective single-center observational longitudinal study was conducted at State Institution «Institute of Nephrology of the National Academy of Medical Sciences» in Kyiv, Ukraine, for between January 2013 and September 2017. The study protocol was confirmed by the Ethics Committee of the Institute. Informed consent was obtained from all the subjects participating in the study.

The patients were eligible for entry when they planned the initiation of PD therapy, and, they were 18 years or older with no clinically significant cardiovascular or infectious diseases on entry. Additionally, the exclusion criteria for study entry were: diabetes mellitus, autoimmune disease, hospitalization in previous 3 months and/or the use of medication which could interfere with plasma leptin (prednisone).

After enrollment, such parameters as the development of PD-related peritonitis, serious cardiovascular events, transfer to hemodialysis or kidney transplantation and death were also included to the exclusion criteria list of our study. A flow chart of the study is presented in Figure 1.

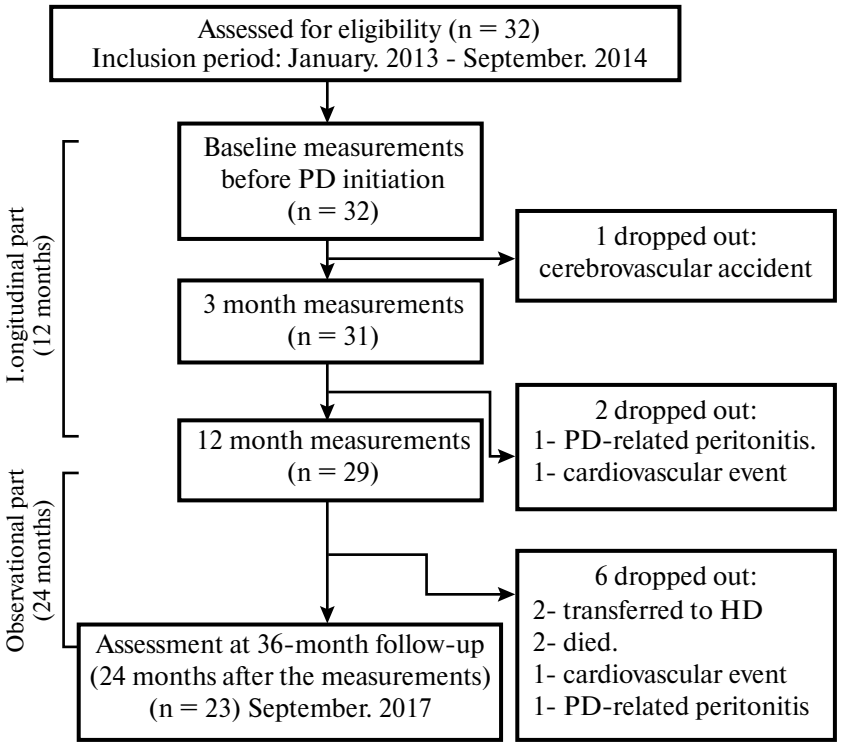

Figure 1. Flow diagram of the study.

All patients underwent continuous ambulatory PD (CAPD). The treatment with CAPD was performed using Dianeal PD 4 with glucose concentration of 1.36% and 2.27%. The recruited PD patients received 4 exchanges daily.

Study measurements were performed at baseline (before PD initiation) and after 3- and 12- month PD treatment. When the work on longitudinal measurements was finished, we continued clinical observation on the cohort of our patients during 2 additional years. The total follow-up period was extended to 36 months.

During this period, 9 patients were dropped out from the study: 3 patients (33.3 %) had non-fatal cardiovascular events, 2 patients (22.2 %) died (the main causes of death were cardiovascular diseases, too), 2 patients (22.2 %) changed dialysis modality and 2 patients (22.2 %) received PD-related peritonitis.

Most patients required antihypertensive medications as well as other drugs commonly used in ESRD, such as phosphate and potassium binders, diuretics, iron supplementation and erythropoietins.

Anthropometric measurements. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Laboratory evaluation. Whole blood samples were collected from the patients after an overnight fast during the time of the routine outpatient visit. The blood samples were processed immediately after sampling. Routine biochemical parameters including blood and daily dialysate concentration of urea and creatinine, serum albumin, C-reactive protein (CRP), cholesterol and glucose were carried out using an automatic analyzer "Flexor junior" (Netherlands). Haematological parameters of blood were determined using an "ABX Micros-60" (France).

The adequacy of dialysis was determined by measuring the total weekly creatinine clearance (CrCl) (which was normalized to 1.73 m2 of the body surface area) and total weekly urea clearance (Kt/V) using the Watson formula for body water [13]. Peritoneal Kt/V and renal Kt/V were estimated separately. The dialysate/plasma creatinine ratio (D/P) was calculated from creatinine concentrations in 24-h dialysate and the plasma.

Along with the standard diagnostic methods, we defined the blood levels of leptin by using an ELISA with DRG Diagnostics kits (Marburg, Germany) according to the manufacturer's protocol.

Statistical analysis. The analysis and all graphs were performed using MedCalc (Belgium). The mean (M) and standard deviation (SD) or the median (Me) and interquartile ranges [Q25 - Q75] were calculated according to a normal distribution. For the statistical analysis, we used the Student's t-test and nonparametric (U-test) Mann-Whitney.

Pearson's or Spearman's (as appropriate) correlation tests were used to evaluate relationships between leptin and clinical or PD adequacy parameters.

Survival analyses with Kaplan-Meier log-rank test and Cox proportional hazard regression were used to examine whether serum leptin level predicted survival for up to a 3 year of follow-up period. PD inadequacy was defined as total weekly Kt/V < 1.7 at the time of the last observation point. The durations of technique survival were calculated from the date of inclusion in the study. For conducting this analysis, in September 2013, the patients were categorized into 2 groups according to baseline leptin level.

P values were calculated, and the null hypothesis was rejected if the P value was <0.05.

Results. A total of 23 patients (15 men and 8 women) with ESRD, who started the treatment with continuous ambulatory peritoneal dialysis (CAPD), were included in the study. The average age of the patient population was 52.4 ± 12.3 years. The main nosological basis of ESRD was glomerulonephritis in 14 patients; 4 patients had hypertensive nephropathy; there were found 2 cases of amyloidosis and 2 cases of obstructive nephropathy; gouty nephropathy was found in 1 patient. Baseline characteristics of the study participants are presented in Table 1.

Table 1

Baseline characteristics of ESRD patients at study entry

Clinical parameters	**The patients (n = 23)**
Male gender, n (%)	15 (65.2%)
Age, years	49.3 ± 12.2
Charlson Comorbidity Index, points	5.8 ± 1.6
BMI, kg/m^2	25.2 ± 4.3
Patients with normal weight, (%)	23 (60.9%)
Overweight patients	9 (31.1%)
Serum albumin, g/L	37.1 [34-39]
CRP, mg/L	9.8 [4.3-17.2]
Systolic blood pressure, mm Hg	131 ± 14.2
Diastolic blood pressure, mm Hg	78 ± 12.4
Hb, g/L	100.6 ± 16.2
Glucose, mmol/L	5.4 ± 2.1
Ferritin, ng/ml	533 [338.5-832.7]
Calcium, mmol/L	2.18 [2.0-2.33]
GFR, mL/min/1.73 m^2	8.5 [4.5-11.5]
Phosphorus, mmol/L	1.8 ± 0.5
iPTH, ng/L	236 [123-389]
Urine volume, mL/24 h	870 [320-1200]
Total cholesterol, mmol/L	4.95 [4.1-6.6]
Medications, n (%)	
ACE inhibitors / RAAS blockers	7 (30.4 %)
Iron supplementation	12 (52.2 %)
Erythropoietins	14 (61.0 %)
Beta-blockers	17 (74 %)
Calcium channel blockers	19 (82.6 %)
Diuretics	8 (34.8 %)
Lipid-lowering therapy	9 (39.1 %)

The values are expressed as mean ± standard deviation (M ± SD) or as median and interquartile range (Me [Q25-Q75]).

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CrCl, creatinine clearance; CRP, C-Reactive Protein; Hb, hemoglobin; iPTH, intact parathyroid hormone; RAAS, renin-angiotensin-aldosterone system.

The median serum leptin concentration at study entry was 10.6 [5.6-21.9] ng/mL. The leptin level and its dynamics during the year after the PD treatment initiation were dependent on body mass index (Table 2, Figure 2).

Table 2

The serum leptin concentration categorized by BMI (ng/mL)

Patients' treatment status	Normal weight (BMI 18.5–24.9 kg/m²)	Overweight or obese (BMI > 25 kg/m²)	p
Before PD initiation	9.4 [4.2-16.5]	20.5 [5.6-37.3]	0.03
After 3-months PD	23.2 [15-25]	31.3 [11.2-85.9]	0.5
After 12-months PD	2.1 [0.9-5.2]	35.1 [6.6-36.4]	0.0001

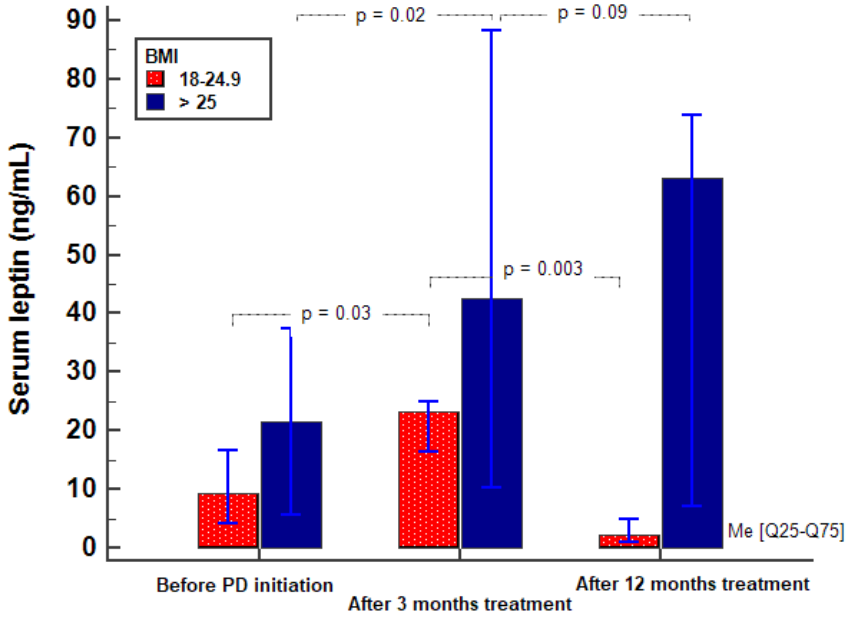

Figure 2. Serum leptin concentrations dynamics in PD patients.

As shown in Figure 3, overweight or obesity patients had ever-increasing leptin levels after 3- and 12-month PD treatment. Whereas in the normal weight PD patients we observed a significant decrease in leptin levels after 12- month PD treatment.

Moreover, serum leptin concentration in the women was significantly higher compared with men (46.4 [1.1-95] vs 9.8 [3.2-14.5] ng/mL; p = 0.02). Blood cholesterol levels had a positive correlation with serum leptin concentrations after 3- and 12-month PD treatment: r = 0.53, p = 0.01 and r = 0.56, p = 0.008, respectively. However, we did not find a statistically significant association of leptin with PD adequacy parameters in the patients after 3- and 12-month PD treatment. Therefore, peritoneal creatinine clearance, total weekly Kt/V and urine volume did not correlate with serum leptin level after 12-month PD treatment (r = -0.2, p = 0.49; r = 0.09, p = 0.6 and r = 0.2, p = 0.34, respectively). No significant correlations between leptin level and other examined parameters were observed.

10 of 23 (43.5 %) patients had total weekly Kt/V <1.7 during the follow-up period of 36 months. At study entry, the patients were stratified according to serum leptin concentrations, namely, below or above the median leptin concentration levels (<10.6; ≥10.6 ng/mL). In the Cox proportional hazard model adjusted for gender, serum leptin level was demonstrated as the effective factor in PD adequacy survival: HR 5.3 (95% CI 1.7; 16.3).

PD adequacy survival was better in the patients with leptin concentrations above the median (≥ 10.6 ng/mL) compared with the patients who had serum leptin levels below the median (log rank test, $\chi 2 = 8.2$; p = 0.0042).

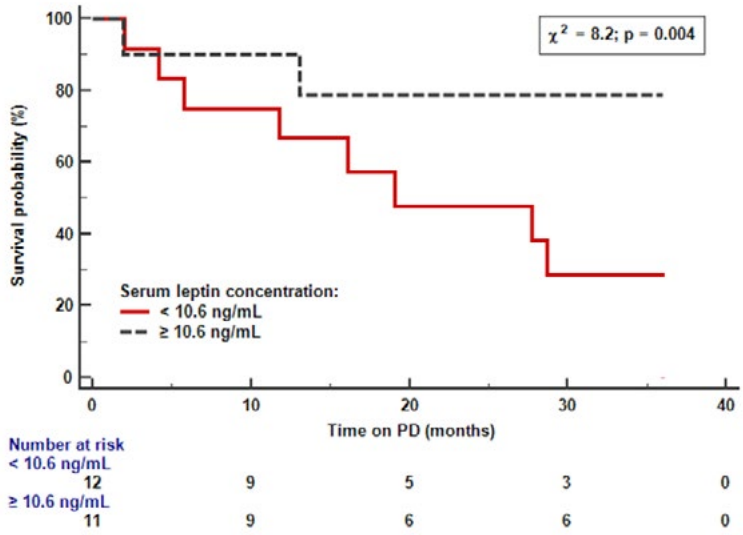

Figure 3. Kaplan–Meier PD adequacy survival curves in the patients dichotomized according to the serum leptin level in the 3-year follow-up.

Discussion. In our study, we investigated the effect of PD initiation on the serum leptin concentration and its relation with PD adequacy. To our knowledge, this study is the first prospective longitudinal study to compare leptin levels during 12 months.

There are few studies on the relationship between blood leptin level and PD survival, but, the results of some research works contradict each other. Golembiewska E et al has demonstrated a negative association between serum leptin levels and dialysis adequacy in newly started PD patients [9]. On the contrary, Scholze A with colleagues have showed significant correlations between low serum leptin concentration and mortality in hemodialysis patients [15].

Similarly to Momeni study [15] we have not observed a significant relationship between PD adequacy parameters and serum leptin level.

Our results support recent studies regarding the importance of leptin levels in PD patients. As well as the majority of previous studies [9, 16-19] the results of our study have demonstrated an increasing level of serum leptin concentration in ESRD patients after PD treatment initiation. Teda D et al showed that a single 6-h dwell with PD4 3.86% glucose acutely increased plasma leptin level [20]. But, it is surprising, that the median leptin level in our patients with normal BMI significantly decreased after 12- month PD therapy. The mechanism of a leptin decrease in normal weight PD patients is still unclear. In our view, it might be resulting from both diminished fat mass and leptin removal by PD [21].

Distinctively ever-increasing serum leptin level in overweight PD patients can be a consequence of altered glucose and fat metabolism which may lead to chronic inflammation, malnutrition and low long-term survival of the patients [17, 18]. On the other hand, hyperleptinemia is reported as the phenomenon of "Reverse Epidemiology" or "Obesity Paradox" in patients with ESRD [22, 23]. In contrast to the general population, where obesity is associated with increased cardiovascular risk and decreased survival, a higher level of BMI is paradoxically associated with better survival in ESRD patients [22, 23]. Snyder et al. [24] performed a retrospective study of 41,197PD patients and found out that overweight and obese participants had a survival benefit compared to those with lower BMI.

The present study is in accordance with the recently advanced concept of "Reverse Epidemiology" in patients with ESRD. Probably, high leptin concentration in PD patients is a more effective and beneficial parameter than a low one which can be due to leptin's capacity of a reducing protective endothelial nitric oxide production [25].

This study has several limitations which have to be pointed out. First, it was a small sample size study performed in a single center; therefore, our findings only revealed associations. Second, lack of adjustment for BMI and other potential factors that can influence the results. Despite its limitations, a strong association observed in the present study has indicated the possibility of leptine to predict PD technique failure. Further greater prospective studies with checking carbohydrate exchange and inflammatory markers are needed to confirm or refute our findings.

Conclusions. Our study have demonstrated markedly elevated serum leptin level in overweight PD patients and its strong decrease during 12 months in patients with normal weight. Low serum leptin level before PD initiation is associated with inadequate PD. Further research are needed to identify the influence of long-term treatment with glucose-containing solutions onto leptin state among PD patients.

Disclosure Statement. The authors declare no conflict of interest.

Financial support. None.

Authors' contributions.

N. Stepanova: was the author of the concept and the design, a major contributor in writing the manuscript; she analyzed and interpreted the patient data.

O. Burdeyna: collected and analyzed the data, prepared the manuscript.

V. Driianska: performed the blood leptin examination.

O. Ablogina: collected the data.

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