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Peritonitis Incidence Was Correlated with Duration of Peritoneal Dialysis Rather than Leptin or Neutrophil to Lymphocyte (N/L) Ratio in Peritoneal Dialysis Patients

Periton Diyaliz Hastalarında Peritonit İnsidansı Nötrofil/Lenfosit Oranı'ndan (N/L) Ziyade Periton Diyaliz Süresi ile Koreledir

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Abstract

Objective: End stage renal disease (ESRD) has a high worldwide prevalence and incidence. Peritonitis is one of the leading causes of hospitalization in peritoneal dialysis patients. Although inflammatory markers show increased inflammatory responses, cellular immune response was decreased in ESRD patients. Leptin is an adipocyte-derived hormone that has activity in energy, nutrition and immune system. Neutrophil to lymphocyte ratio (N/L) was emerged as a predictive and prognostic criterion in many instances. In this study, we aimed to investigate the relationships between increased inflammation in peritoneal dialysis patients and leptin, N/L ratio.

Materials and Methods: Forty-one ESRD patients, who were been at least 12 months of peritoneal dialysis therapy, were included in the study. Patients' demographic properties were recorded. Serum leptin level, WBC count, C-reactive protein, erythrocyte sedimentation rate and biochemical markers were measured. Patients with active viral or bacterial infection, malignancy, inflammatory disease, immunosuppressive medication users were all excluded from the study. Age and sex-matched healthy control group was included in the study only for their leptin levels.

Results: The measured mean serum leptin level of the patient group was statistically significantly higher than control group (1624.88±1608.16 and 416±439.85). The calculated mean peritonitis incidence was 0.041±0.047 peritonitis/per year. The number of peritonitis attack was significantly correlated with duration of peritoneal dialysis, body mass index (BMI), age and presence of cardiovascular disease. Serum leptin level was significantly correlated with sex, age, primary cause of ESRD, BMI, blood glucose level and duration of peritoneal dialysis (PD).

Conclusion: We detected that ESRD patients have higher serum leptin levels compare to healthy adults. Increased leptin was correlated with sex, age, BMI, primary cause of ESRD and serum glucose level. Number of peritonitis attack and peritonitis incidence was significantly correlated with the duration of PD, BMI and sex. We weren't able to show the predictive N/L value in PD patients in case of peritonitis.

Key Words: Leptin, neutrophil to Lymphocyte raito, peritonitis, peritoneal dialysis

Özet

Amaç: Son dönem böbrek yetersizliği (SDBY) dünya genelinde yüksek bir prevelansa sahiptir. Peritonit, periton diyaliz hastalarının hastane yatış sebepleri arasında en önde gelenlerden bir tanesidir. SDBY hastalarında inflammatuvar belirteçler artmış inflamatuvar yanıt varlığını gösterse de hücresel ve immün yanıt azalmıştır. Adiposit kaynaklı bir hormone olan leptin, enerji, beslenme ve immün sistem üzerinde etkilere sahiptir. Nötrofil-lenfosit oranı (N/L) çeşitli durumlarda prediktif ve prognostik kriter olarak ortaya çıkmıştır. Biz bu çalışmada periton diyaliz hastalarında artmış enflammasyon, leptin ve N/L ilişkisini araştırmak istedik.

Gereç ve Yöntem: En az 12 aydan beri periton diyalizi yapan 41 SDBY hastası çalışmaya dahil edildi. Hastaların demografik özellikleri kayıt edildi. Serum leptin düzeyi, lökosit sayısı, C-reaktif protein, eritrosit sedimentasyon hızı ve biyokimyasal test sonuçları kayıt edildi. Aktif viral veya bakteriyel enfeksiyon, maliginite, inflammatuvar hastalık veya immünsüpresif tedavi almakta olan hastalar çalışma dışı bırakıldı. Serum leptin düzeyinin karşılaştırılması amacıyla çalışmaya yaş ve cinsiyet uyumlu kontrol grubu dahil edildi.

Bulgular: Hasta grubunda ölçülen serum leptin düzeyi control grubundan istatistiksel olarak anlamlı yüksek bulundu (1624.88±1608.16 and 416±439.85). Hesaplanan peritonit insidansı 0.041±0.047 peritoniti/ hasta yılı olarak bulundu. Peritonit atağı sayısı; periton diyalizinin süresi, beden kitle indeksi (BKİ), yaş ve cardiovasküler hastalık varlığı parametreleri ile sitatistiksel açıdan anlamlı korelasyon göstermekteydi. Serum leptin düzeyi; cinsiyet, yaş, SDBY primer sebebi, BKİ, kan glikoz seviyesi ve periton diyalizinin süresi ile anlamlı korelasyon gösterdiği tespit edildi.

Sonuç: Son dönem böbrek yetmezliği hastalarının sağlıklı yetişkinlere göre daha yüksek leptin düzeyine sahip olduğunu tespit ettik. Leptin düzeyindeki artış cinsiyet, yaş, BKİ, SDBY'nin primer sebebi ve serum glukoz düzeyi gibi parametrelerle istatistiksel olarak anlamlı ilişkiye sahip olduğu tespit edildi. Peritonit atak sayısı ve peritonit insidansının periton diyalizi (PD) süresi, BKİ ve cinsiyet ile anlamlı ilişkli olduğu bulundu. N/L oranının peritonit açısından PD hastalarında prediktif bir değerinin olduğu gösterilemedi.

Anahtar Kelimeler: Leptin, nötrofil lenfosit oranı, peritonit, periton diyalizi

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Introduction

Chronic renal failure has a high worldwide prevalence and incidence. Long-term dialysis patients have high morbidity and mortality rates. Associated risk factors were age, gender, duration of dialysis, concomitant diseases, presence of complication and inflammatory diseases. Hospitalization requirement is more frequent and duration is longer in dialysis patients especially in patients with comorbid infection and cardiovascular disease [1]. Peritonitis is one of the leading causes of hospitalization in peritoneal dialysis patients [2].

Immune system functions were affected in uremia. Inflammatory markers show an increased inflammatory response however cellular immune response was decreased in ESRD patients [3]. Increased inflammation was accused for increasing cardiovascular morbidity and mortality of ESRD patients [4]. Leptin is a protein for body composition that has a regulatory role controlling apatite and energy expenditure. Serum leptin level increases in obesity, hyperglycaemia and uremia due to decreased renal excretion [5, 6]. In this study we aimed to detect a possible relation between peritonitis incidence and serum leptin level and neutrophil to lymphocyte ratio (N/L) in ESRD patients who were treated with continuous peritoneal dialysis.

Materials and Methods

In this study, patients were selected from the outpatient clinic of Ataturk University Medical Faculty Nephrology Department between August 2012 and November 2012. The study was approved by the local ethical committee. Informed consent of the patient and control groups was collected from the previous study. Forty-one ESRD patients (17 male, 24 female), who were on least 12 months of peritoneal dialysis treatment, were included in the study. Patients with known active viral or bacterial infection, malignancy, inflammatory disease and immunosuppressive medication users were all excluded from the study. Patients whose white blood cell count was over 12000198^3/mL were also excluded from the study due to possible infection, inflammation or hematologic disease. 30 (14 male, 16 female) age and sex-matched control healthy subject serving as the control group for serum leptin level were included in the study.

Blood samples for leptin, whole blood count, C reactive protein (CRP), Erythrocyte sedimentation rate (ESR), glucose, albumin and calcium (Ca), albumin were collected from forearm venipuncture in the morning. Whole blood count and all other laboratory measurements except leptin were done within 30 to 60 min after sampling. Whole blood count was done using the Beckman Coulter LH 750 (USA) with commercial kits.

Quetelet index or Body mass indexes (BMI) were calculated according to patients' actual weight and height at the time of venipuncture using the weight/height^2 formula [7].

Human serum leptin analysis

Leptin analysis was performed according to manufacturer manuals. Samples for serum leptin were centrifuged at 1000 rpm for 15 min within 30 minutes after collection. Supernatant serum samples were stored at -20 C° till the analysis. Serum leptin levels were analyzed using the Boster's Human leptin ELISA kit. Aliquot 0.1 mL per well of the 4000pg/mL. 0.1 mL diluted human serum sample added and incubated at 37°C for 90 min. Anti-human leptin antibody added and incubated for 60 min. Plates were washed three times using the TBS solution. 0.1 mL of Avidin-Biotin-Peroxidase Complex (ABC) added to each well and incubated for 30 min. The plates were washed using the TBS solution. 90 µl TMB color developing agent added to each well and incubated for 15 min at dark. 0.1 mL TMB stop solution added. Absorbance was analyzed at 450 nm 30 min after stop solution added.

Blood glucose, serum albumin, Ca, P, ESR, CRP was analyzed in a routine laboratory.

Patient characteristics, duration of peritoneal dialysis (months), presence of any concomitant diseases, age, gender, sex, number of peritonitis attack, if available cultured microorganism, etiologic cause of ESRD, body mas index, erythrocyte sedimentation rate, C-reactive protein level, white blood cell count, formulation of subgroups of white blood cell (neutrophil, lymphocyte), neutrophil to lymphocyte ratio, blood glucose, calcium, phosphate and albumin levels were all recorded.

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS) 20.0 for Windows (SPSS Inc, Chicago, Illinois, USA) was used to analyze the data. Parametric tests were applied to data with normal distribution, whereas nonparametric tests were applied to data with non-normal distribution. Chi-square tests were applied for categorical variables. One-way ANOVA test and Kruskal-Wallis One-Way Analysis of Variance on Ranks Test were applied to determine the difference between independent groups. In addition, The Tukey HSD and Dunn's Post Hoc Tests were applied to check the differences. The relationships among the variables were evaluated using the Pearson and Spearman's rho correlation analysis. Results were expressed as mean±SD and median (interquartile range), and p value <0.05 was considered statistically significant.

Results

Fort-one ESRD patients, who were on least 12-month therapy of peritoneal dialysis, were included in the study serving

Table 1. Descriptive properties of the patient group and summary of the results

	n	Minimum	Maximum	Mean	Std. deviation
Age (Patient) control	41	18	80	48.41	15.67
	30	21	77	36.93	15.27
Duration of peritoneal dialysis	41	8	100	37.78	24.60
BMI (Patient) kg/m^2	41	18	37	23.85	4.411
Peritonitis attack (#)	41	0	7	1.49	1.719
Peritonitis incidence /year	41	0.00	0.159	0.04192	0.04718
WBC198^3/mL	41	3600	11300	7000.00	2089.37
ESR mm/h	39	9	60	32.00	13.85
CRP mg/dL	41	2.90	24.00	5.77	5.33
LEPTIN (pg/mL) patient group	41	62.50	4000.00	1624.88	1068.16
LEPTIN (pg/mL) Control group	30	62.50	1568.76	416.01	439.85
Calcium	41	6.10	10.40	9.0707	0.84269
Phosphor	41	1.60	8.70	5.20	1.49
Albumin gr/dL	41	2.10	4.60	3.4293	0.55644
Glucose mg/dL	41	54.00	238.00	103.80	37.874
N/L	41	0.1	10.0	3.32	1.71

WBC: white blood cell count; BMI: body mass index; N/L: neutrophil to lymphocyte ratio; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

as the patient group and 30 healthy subjects were included in the study serving as the control group. Characteristic properties of the patient group and summary of the results as means and standard deviation were given in Table 1. The frequencies of the primary causes of ESRD from the most common to rare among the patients were hypertension, diabetes mellitus (DM), glomerulonephritis, other causes, chronic interstitial nephritis and polycystic renal disease (29.2%, 17.2%, 17.1%, 17.1%, 14.6%, 7.3% respectively).

Patients with known active viral or bacterial infection, malignancy and inflammatory disease and immunosuppressive medication users were all excluded from the study because the investigated subject was also about inflammatory markers. Because of this reason the patients with inflammation were excluded.

The calculated peritonitis incidence was 0.041±0.047 peritonitis attack per year (total number or peritonitis attack was 58 and total follow-up period was 1550 months). Causative bacterial organism had isolated in 60.09% of peritonitis attacks. BMI in the female patients were statistically significantly higher than in male patients p=0.03 (24.21±5.21, 23.35±3.01 respectively). Also, the number of peritonitis attack in female patients was statistically significantly detected higher than in males (1.83±1.99, 1.00±1.11 respectively) but there was no significant difference detected in peritonitis incidence per year between female and male patients (p>0.05). Serum leptin level in female patients was also detected statistically significantly higher than in male patients p<0.000 (2398.08±1669.52, 578.78±670.18 respectively).

BMI index in patients with DM and/or HT as a cause of primary disease of ESRD had statistically significantly higher than in patients with other primary causes of ESRD, p=0.013 (26.03±5.2, 22.15±2.73 respectively). ESR level in patients with DM and /or HT were also detected statistically significantly higher than in resting patients p=0.036 (33.13±18.55, 31.36±11.10 respectively). There is no statistically significant difference detected between patients with DM and/or HT and the patients with other causes of ESRD among the age, duration of peritoneal dialysis, CRP, serum leptin level, number of peritonitis, peritonitis incidence, albumin and N/L ratio.

It was detected that the number of peritonitis attack was significantly correlated with the duration of peritoneal dialysis, BMI, age and presence of cardiovascular disease (p=0.023, p=0.009, p=0.048, p=0.037 respectively).

Neutrophil to Lymphocyte ratio (N/L) was detected statistically significantly correlated only with sex of the patient (p=0.007). CRP was correlated with albumin level, ESR and Ca (p=0.15, p=0.049, p=0.23 respectively) ESR was statistically significantly correlated with blood glucose level (p=0.002). Mean blood glucose level of the patients was detected as 103.8±37.87. It was statistically significantly correlated with serum leptin level, age of the patient, primary cause of ESRD, ESR and albumin (p=0.021, p=0.001, p=0.008, p=0.002, p=0.009 respectively). Summary of the statistical results were given in Table 2.

Table 2. Summary of the statistical test results

		n	Mean	Std. deviation	p
BMI kg/m^2	Male	17	23.35	3.01	0.039
	Female	24	24.21	5.21	
	DM±HT	18	26.03	5.20	0.013
	OC	23	22.15	2.73	
Peritonitis attack	Male	17	1.00	1.11	0.008
	Female	24	1.83	1.99	
Serum leptin level (pg/mL)	Male	17	578.78	670.18	0.014
	Female	24	2398.08	1669.52	
ESR (mm/h)	DM±HT	17	33.13	18.55	0.036
	OC	22	31.36	11.10	
Glucose (mg/dL)	DM±HT	18	119.05	47.76	0.002
	OC	23	91.86	22.48	
Age	Male	17	46.82	15.47	0.572
	Female	24	46.96	16.47	
Duration of peritoneal dialysis (moth)	Male	17	30.41	21.08	0.206
	Female	24	44.71	25.59	
Presence of CVD	Male	17	1.47	0.51	0.081
	Female	24	1.71	0.46	
CRP (mg/dL)	Male	17	5.67	5.48	0.933
	Female	24	5.83	5.35	
Albumin (g/dL)	Male	17	3.48	0.71	
	Female	24	3.39	0.42	0.064
Glucose (mg/dL)	Male	17	96.41	37.19	0.477
	Female	24	109.04	38.25	

WBC: white blood cell count; BMI: body mass index; N/L: neutrophil to lymphocyte ratio; ESR: erythrocyte sedimentation rate; CRP: C- reactive protein; DM: diabetes mellitus; HT: hypertension; CVD: cardiovascular disease

The mean serum leptin level of the patient and control groups were 1624.88±1608.16 (62.5-4000.0) and 416±439.85 (62.5-1568.76) respectively. The mean serum leptin level of the patient group was statistically significantly higher than control group ($p<0.001$). There is a statistically significant correlation between serum leptin level and sex, age, primary cause of ESRD, BMI and blood glucose level, duration of PD ($p<0.001$, $p=0.001$, $p=0.021$, $p<0.000$, $p=0.017$, $p=0.038$ respectively). Serum leptin level in peritoneal dialysis patients with DM and/or hypertension was significantly higher than in patients with glomerulonephritis or other primary causes of end stage renal disease (Figure 1).

Discussion

Peritonitis is one of the most common complications of PD. Besides being the most frequent cause of hospitalization in patients receiving PD, it is also the major factor that leads to catheter loss. In this study, the number of peritonitis attack was detected significantly correlated with the duration of peritoneal dialysis, and BMI of peritoneal dialysis patients. Also it was detected that patients with known cardiovascular disease (CVD) tend to have higher incidence of peritonitis ($p=0.037$). The accused risk factors that increase the risk of peritonitis were hypoalbuminemia, constipation, amyloidosis, surgical catheter replacement in PD, exit-site infection, immunosuppression and comorbid diseases [8]. Although PD has a survival advantage in the first 3-5 years of therapy compare to hemodialysis (HD), this survival benefit was fade down in later years of follow up. Fibrosis and new vessel formation caused by chronic inflammation in peritoneal cavity via PD solutions leads to thickening of peritoneal membrane [9]. Both immune activation and immune deficiency were simultaneously present in end stage renal disease (ESRD) patients. Increased systemic inflammation leads to cardiovascular disease, cerebrovascular disease and mortality, and

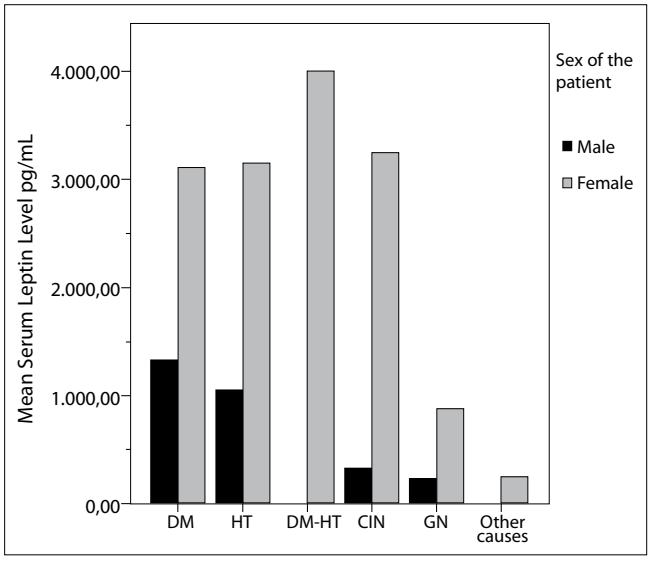

Figure 1. *Mean Serum Leptin level of the Patients According to Primary Causes of ESRD of The Peritoneal Dialysis Patients.*
ESRD: end stage renal disease

on the other hand immune deficiency leads to impaired response to vaccination and poor outcome of microbial infections [10, 11].

Soluble factors of immune system and their ancestry cellular parents comprise a complex set of interaction to defend the host against various diseases and conditions. The basic affair is the inflammations, which cause destruction and damage as a response to infection and tissue damage. Leptin is an adipocyte-derived satiety hormone and also known as pro-inflammatory cytokine, which is a large-molecular weight protein. It is also noted as uremic toxin, because serum leptin concentrations are significantly higher in hemodialysis patients and it cannot be removed by hemodiafiltration. Leptin mediates an anti-apatite role via specific receptors in brain and peripheral tissue. Leptin has also emerged as a potential mediator of inflammatory status and a positive modulator of IL-1α, TNF-α and IL-6 secretion. Leptin also increases IFN-γ, producing Th1 polarized cells and exerts its bioactivity at developmental, proliferation and activation levels [12-15]. In our study we detected that serum leptin level in peritoneal dialysis patients were significantly higher than in control group. Also serum leptin level in PD patients is significantly correlated with sex, age, BMI, primary casue of ESRD and serum glucose level. According to the subgroup analysis, we detected that patients with diabetes mellitus or hypertension as a primary cause of ESRD had significantly higher serum leptin level compare to other causes of ESRD.

Neutrophil to lymphocyte ratio (N/L) was reported as an independent inflammatory marker to predict adverse outcome in many medical and surgical conditions [16, 17]. Especially in chronic inflammatory diseases like diabetic nephropathy, cardiovascular disease, inflammatory bowel disease, colon and pancreas caner [18, 19]. PD is also a chronic inflammatory state and high basal inflammation even further increased in case of peritonitis. Besides, N/L has a predictive value. Recently it has been showed that N/L had prognostic value in inflammatory conditions. In this study although PD patients had increased the inflammatory state together with other risk factors such as CVD, DM and HT we have not detect any significant correlation between N/L and other inflammatory parameters.

Our study has limitations to answer all questions about peritonitis, leptin and N/L. First of all, this is a cross-sectional study and it is not adequate to detect causes and response relationships accurately. Although the number of the patients is adequate for a single study, the patient group is heterogenius for primary causes and further studies with larger number of patients are needed to detect differences between subgroups of ESRD.

In conclusion, we detected that ESRD patients have higher serum leptin levels compare to healthy adults. Increased leptin is correlated with sex, age, BMI, primary cause of ESRD and serum glucose level. The number of peritonitis attack and peritonitis incidence was significantly correlated with duration of PD, BMI and sex of the patient. We were not able to show predictive N/L and leptin values in PD patients in case of peritonitis. Further larger scaled prospective studies are required to reveal relation of lymphocyte functions and leptin in ESRD patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of Atatürk University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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