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The Relation of Circulating Levels of Leptin with Cognition in Patients with Alzheimer's Disease

Alzheimer Hastalarında Serum Leptin Düzeyleri ve Kognisyon İlişkisi

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ABSTRACT

Introduction: To investigate the relation of circulating levels of leptin with cognition in Alzheimer's disease (AD) patients.

Methods: Thirty patients meeting the clinical diagnostic criteria for AD, and twenty-five healthy controls were enrolled into the study. At baseline, all patients underwent standing height, weight measurements, and waist circumference (in centimeters) using a standard scale. Body mass index (BMI) was then calculated as weight (in kilograms). A single 5-ml fasting blood sample was obtained from each patient. All subjects were evaluated by Turkish version of Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR) and Global Deterioration Scale (GDS).

Results: The mean age of patients and controls were 72.33±10.11 and 67.20±8.95, respectively. There was not any significant difference between age of the patients and the controls (p=0.054). Both patient and control groups consisted of mostly women (60% and 56% respectively). The mean waist circumferences (WC) of patients and controls were 95.46±10.87 and 97.76±10.07, respectively and was not statistically different (p=0.424). The mean serum leptin levels in patients and controls were 5.49±4.06 ng/dL 5.71±4.45 ng/dL, respectively. Leptin levels were not statistically different between patients and controls (p=0.84). The mean MMSE scores of AD patients and controls were 17±6.54 and 27.32±2.15 respectively, and AD patients had significantly lower MMSE scores than the controls (p=0.000). The mean BMI of patients and controls were 25.72±3.98 and 27.92±3.08 respectively. The BMI of controls were higher than patients and there was statistically significant difference between two groups (p=0.029). In the patient group, there were no correlations between leptin levels and age (p=0.067), BMI (p=0.098), WC (p=0.113), MMSE (p=0.203), CDR (p=0.519) and GDS (p=0.587). Similarly in control group leptin levels were not correlated with BMI (p=0.718), WC (p=0.755) and MMSE (p=0.859).

Conclusion: In the present study, we could not find any relation between blood leptin levels and cognition in AD patients.

Keywords: Alzheimer's disease, leptin, cognition

ÖZ

Amaç: Alzheimer hastalarında (AH) serum leptin düzeyleri ve kognisyon ilişkisini incelemek.

Yöntem: Klinik olarak AH tanısı almış otuz hasta ve yirmi beş sağlıklı kontrol çalışmaya alındı. Başlangıçta her hastanın standart boy, ağırlık ve bel çevresi (BÇ) ölçümleri alındı. Vücut kitle indeksi (VKİ), ağırlık ve boy değerleri kullanılarak hesaplandı. Her katılımcıdan 5 mL açlık kan örneği, bir kereye mahsus olmak üzere alındı. Tüm katılımcılar Mini Mental Durum Değerlendirme Testinin (MMSE) Türkçe versiyonu, Klinik Demans Derecelendirme Ölçeği (CDR) ve Global Bozulma Ölçeği (GDS) uygulanarak değerlendirildi.

Bulgular: Hasta ve kontrollerin yaş ortalaması sırasıyla 72,33±10,11 ve 67,20±8,95'ti. Hasta ve kontrol grubu yaş ortalaması arasında istatistiki açıdan anlamlı fark yoktu (p=0,054). Hasta ve kontrol grubunun çoğunluğunu kadınlar oluşturuyordu (sırasıyla %60 ve %56). Hasta ve kontrollerin ortalama bel çevreleri sırasıyla 95,46±10,87 ve 97,76±10,07 olarak bulundu ve aralarında istatistiksel açıdan anlamlı fark saptanmadı (p=0,424). Hasta ve kontrollerin ortalama serum leptin düzeyleri sırasıyla 5,49±4,06 ng/dL ve 5,71±4,45 ng/dL olarak bulundu. Leptin düzeyleri açısından anlamlı fark saptanmadı (p=0,84). Ortalama MMSE skorları sırasıyla 17±6,54 ve 27,32±2,5 olarak bulundu ve anlamlı istatistiki fark vardı (p=0,000). VKİ değerleri hasta ve kontrol grubunda sırasıyla 25,72±3,98 ve 27,92±3,08 olarak bulundu ve kontrol grubunun VKİ değerleri hasta grubundan anlamlı yüksek bulundu (p=0,029). Hasta grubunda leptin düzeyleri ile yaş (p=0,067), VKİ (p=0,098), BÇ (p=0,113), MMSE (p=0,203), CDR (p=0,519) ve GDS (p=0,587) arasında istatistiksel açıdan anlamlı ilişki saptanmadı. Benzer şekilde, kontrol grubunda da leptin düzeyleri ile VKİ (p=0,718), BÇ (p=0,755) ve MMSE (p=0,859) arasında anlamlı ilişki bulunmadı.

Sonuç: Biz bu çalışmada, Alzheimer hastalarında serum leptin düzeyleri ile kognisyon arasında bir ilişki tespit edemedik.

Anahtar Kelimeler: Alzheimer hastalığı, leptin, kognisyon

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INTRODUCTION

Alzheimer disease (AD) is a pathologically complicated disease including oxidative stress, cell-cycle changes, neurofibrillary tangle, and amyloid-beta formation together with many other biochemical changes that play important role in disease development (1). In longitudinal studies, it has been reported that a lot of biomarkers including serum levels of leptin can be used as a predicting factor in the development of AD (2, 3). In Western societies life expectancy is increasing steadily, and as a consequence more individuals are suffering from age-related disorders such as AD (4).

Although significant advances have been made in recent years, our understanding of the principle cellular changes that occur in the initial stages of this disease, and the means to identify these changes clinically are limited. Thus, key research priorities are to determine the key cellular events that underlie the development and pathogenesis of AD, and to identify possible biomarkers associated with the early stages of AD. Leptin is a novel and promising molecule in research that may link body weight (BW), body mass index (BMI), and neurodegenerative diseases (5, 6). Since the discovery of leptin in 1994 (7), major advances have been made in understanding the neuroendocrine mechanisms regulating appetite, adiposity, obesity, metabolism, sympathetic tone, blood pressure, inflammation, and the hematopoietic and immune systems.

Recently it has been hypothesized that leptin plays an important role in the development of histopathologic features of AD in addition to many genetic and environmental factor. The common opinion in this hypotheses focuses on the slowing down effect of leptin on amyloid plaque and neurofibrillary tangle formation which are the major histopathologic findings of AD (8, 9). There is substantial evidence that leptin modulates Aβ production and metabolism. Chronic peripheral leptin administration in mice has been reported to reduce the brain Aβ levels (10). Moreover, leptin also decreases the BACE1 (β-site APP cleaving enzyme 1) activity in SH-SY5Y cell line (10). Leptin decreases tau phosphorylation explicitly at rat primary cortical neurons (11, 12). It also increases synaptogenesis and aids in memory formation in the hippocampus (13), and has been shown to convert short term potentiation (STP) into long term potentiation (LTP) in hippocampal cultures and hippocampal slices (14). Recent evidence suggests that leptin facilitates spatial learning and memory (15), and also increases neurogenesis in the dentate gyrus of adult mice (16). Recent epidemiological studies have also implicated decreased leptin levels in the pathogenesis of AD. In the prospective study of Framingham, 785 subjects were followed between 1990 and 1994 from the original Framingham cohort (17), and they concluded that leptin levels were inversely related to the risk of developing dementia of the Alzheimer type (17).

In this study we aimed to evaluate the relation of leptin with cognition in AD patients.

METHODS

Thirty patients (18 women and 12 men) with a diagnosis of 'probable AD' according to NINCDS-ADRDA diagnostic criteria and 25 healthy controls (14 women and 11 men) were included in the study. In patient and control groups those with systemic illnesses such as diabetes, thyroid disease, and neoplasia, those with psychiatric diseases (psychosis and severe depression), those using any medication that may affect body weight, and who had major dietary restrictions were excluded. At clinical appointment, all patients underwent body composition measurements and blood sampling. The body composition measurements included body weight (BW; measured to the nearest 0.1 kg with the subject wearing a layer of clothing over underwear), height (measured using a wall-mounted ruler and horizontal bar to the nearest 0.1 cm without shoes), waist circumference (WC), and body mass index (BMI). BMI was calculated by dividing a direct weight measurement (in kilograms) by the squared average of at least two height measurements (in millimeters, converted to meters). The stage of the AD was assessed by using Clinical Dementia Rating Scale (CDR) and Global Deterioration Scale (GDS). All subjects were evaluated by Standardized Mini Mental State Examination Scale (MMSE) by the same clinician. A single 5-mL fasting venous blood sample was collected from each subject between 7:00 and 11:00 am. Serum was separated within 30 min, and stored at 80°C until analysis for level of total leptin. Serum leptin concentrations were measured using the DIAsource ImmunoAssays Human Leptin ELISA kit (DIAsource, Nivelles, Belgium, catalogue number: KAP2281). This ELISA sandwiches human leptin between two monoclonal antibodies reacting against different epitopes on the leptin molecule.

The study protocol was approved by the Institutional Review Board. Informed consent was obtained from all subjects.

Statistical Analysis

All statistical analysis was performed using SPSS software (Statistical Programs for Social Sciences, version 15.0; IBM, Chicago, IL). The independent sample t-test was used for between-group comparisons. All *P* values were two-sided and the level of statistical significance was set at $p<0.05$.

RESULTS

The mean age of patients and controls were 72.33±10.11 and 67.20±8.95, respectively. There was not any statistically significant difference between the age of the patients and the controls (p=0.054). The study group was consisted of mostly women (60% in patient and 56% in control group). The mean waist circumferences (WC) of patients and controls were 95.46±10.87 and 97.76±10.07 respectively, and did not differ between two groups (p=0.424). The mean serum leptin levels in patients and controls were 5.49±4.06 ng/dL and 5.71±4.45 ng/dL respectively. Leptin levels did not differ between the patients and controls (p=0.84). The mean MMSE scores of AD patients and controls were 17±6.54 and 27.32±2.15 respectively, and AD patients had significantly lower MMSE scores than the controls (p=0.000). The mean BMI of patients and controls were 25.72±3.98 and 27.92±3.08 respectively. There was a statistically significant difference between groups (p=0.029) and BMI of controls was higher than patients. Demographic features, body measurements, leptin levels, and MMSE scores of the study group are shown in Table 1. In patient group, there was no correlation between leptin levels and age (p=0.067), BMI (p=0.098), WC (p=0.113), MMSE (p=0.203), CDR (p=0.519), and GDS (p=0.587) (Table 2). In control group, similarly there was not any correlation between leptin levels and BMI (p=0.718), WC (p=0.755) and MMSE (p=0.859). We defined the patient group in the base of GDS

Table 1. Demographic features body measurements, leptin levels and cognitive tests of the study group

	Patient (n=30)	Control (n=25)	p
Gender	**Male (n=12) Female (n=18)**	**Male (n=11) Female (n=14)**	
Age	72.33±10.11	67.20±8.95	P=0.054
WC (cm)	95.46±10.87	97.76±10.07	P=0.424
Leptin (ng/dl)	5.49±4.06	5.71±4.45	P=0.84
MMSE	17±6.54	27.32±2.15	P=0.000
BMI	25.72±3.98	27.92±3.08	P=0.029

p<0.05 is defined as statistically significant, independent sample t-test was used for group comparisons.
WC, waist circumference; MMSE, mini mental state examination; BMI, basal metabolic index.

Table 2. The correlation of leptin levels with body measurements and cognition

	Patient	Control
BMI	p=0.098 r=0.014	p=0.718 r=0.800
WC	p=0.113 r=0.254	p=0.775 r=0.817
MMSE	p=0.203 r=0.582	p=0.859 r=0.601
CDR	p=0.519 r=0.886	
GDS	p=0.587 r=0.688	

Correlation analysis was done by using Spearman's rank correlation coefficient (r). p<0.05 is significant.
BMI, basal metabolic index; WC, waist circumference; MMSE, mini mental state examination; CDR, clinical dementia rating; GDS, global deterioration scale.

such as Group 1 including patients GDS scores <5 (leptin level=5.46±4.16 ng/dL), and Group 2 including patients GDS >4 (leptin level=5.59±4.02 ng/dL). We could not also find any statistical difference in leptin levels between these two groups (p=0.942).

DISCUSSION

It is well established that the adipocyte-derived polypeptide hormone leptin is an important circulating satiety factor that regulates body weight and food intake via its actions on specific hypothalamic nuclei (18, 19). Leptin concentrations may be considered a marker for the extent of body weight, obesity, and fat mass in humans. Excessive body fat accumulation and obesity are associated with increased levels of leptin in previous studies (20). In both AD patients and controls, we could not find any relation of BMI with leptin levels in our study. There is growing evidence that leptin receptors are also widely expressed throughout the brain. In addition to its role in energy homeostasis, leptin seems to play an additional role as a neurotrophic factor that is involved in hippocampal plasticity, and in a number of neurodegenerative diseases (21). Recent laboratory studies investigating the relationship of leptin with the pathogenesis of AD have exhibited new findings that may give rise to new treatment options. Leptin decreases beta-secretase (an enzyme that converts amyloid precursor protein to beta-amyloid) activity in neurons, increases APOE dependent beta-amyloid uptake, and helps beta-amyloid clearance from the brain by binding megalin/lrp2 receptor complex (receptor that is responsible for the beta-amyloid endocytosis) (22). Leptin also inhibits amyloidogenic pathway by preventing lipid accumulation, and decrease tau phosphorylation and neurofibrillary tangle formation by inhibiting gsk-3b enzyme (a kind of tau kinase) (10, 11, 23, 24). It is also well established that learning and memory is a key function of hippocampus and one type of plasticity called as long-term potentiation takes place in this area of brain. It is shown that direct administration of leptin into the hippocampus improves learning and memory performance (25, 26). Indeed, reductions in circulating levels of leptin have been detected in AD patients (27). Leptin has neuroprotective actions, by inhibiting apoptotic cell death, attenuating cell death, improving cell survival, protecting against glutamatergic cytotoxicity, protecting against oxidative stress and promoting the proliferation of hippocampal progenitor cells (28, 29). In follow-up studies including many volunteers, it was shown that individuals whose basal serum leptin levels were in the lowest quarter had the probability of developing AD as high as four-fold than individuals with basal serum leptin levels in the highest quarter (17). In a recent study from Netherland, Teunissen et al. compared basal serum leptin levels in non-obese patients diagnosed as AD and vascular dementia with non-obese controls and they could not find any statistical difference between two groups, and they concluded that peripheral leptin levels do not play a role in evolution of AD pathology similar to our study (29). There are also some studies about the relation of weight loss, body fat mass, satiety with blood leptin levels in Parkinson's disease patients (30–33).

We could not find any relation between leptin levels and cognition, or the severity of the disease in AD patients. In contrary to previous studies (30–35) which revealed positive correlations between leptin levels, BMI, BW and WC, we could not find any correlation with leptin levels and body measurements either.

Our study has a small sample size, and is an observational study. Also, according to the experimentally proven clear role of leptin in AD pathology which has been summarized above, it is also clear that, there are so many factors affecting leptin metabolism. Serum levels of leptin may not be the sole factor which is related to AD's clinical and histopathologic severity.

In conclusion, we need larger sized longitudinal studies to make a decision about its effect on cognition in patients not only in AD, but also in different types of diseases causing any type of cognitive deficits.

Ethics Committee Approval: The study protocol was approved by the Institutional Review Board.

Informed Consent: Informed consent was obtained from all subjects.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - MÜ, GK; Design - MÜ, GK; Supervision - MÜ, GK; Resource - MÜ, GK; Materials - MÜ, GK; Data Collection and/ or Processing - MÜ, GK; Analysis and/or Interpretation - MÜ, GK; Literature Search - MÜ, GK; Writing - MÜ, GK; Critical Reviews - MÜ, GK.

Conflict of Interest: No conflict of interest was declared by the authors.

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Hasta Onamı: Tüm konularda bilgilendirilmiş onam alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

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