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Research Article / Araştırma Makalesi

# *Association Between Serum Netrin-1 Level and Obesity-related Markers in Obese Subjets*

*Obez Bireylerde Serum Netrin-1 Düzeyi ve Obezite ile İlgili Belirteçler Arasındaki İlişki*

**Çiğdem AYDIN ACAR[1,2*], Niyazi AYDIN[2], Suray PEHLİVANOĞLU[3], Mehmet KOK[4]**

[1]Burdur Mehmet Akif Ersoy University, Bucak School of Health, Department of Nursing, Burdur Turkey
[2]Burdur Mehmet Akif Ersoy University, Institute of Health Sciences, Department of Health and Biomedical Sciences, Burdur, Turkey
[3]Necmettin Erbakan University, Faculty of Sciences, Department of Molecular Biology and Genetics, Konya, Turkey
[4]University of Health Sciences Antalya Training and Research Hospital, Department of Internal Medicine, Antalya, Turkey

**Abstract:** Netrins are important signaling proteins that guide both neural and vascular development. Netrin-1 regulates many physiological processes such as cell proliferation, adhesion and migration. The aim of this study was to determine the association between serum netrin-1 level and biochemical parameters in obese subjects. Serum samples were collected from obese (n=15) and control (n=30) subjects. The serum netrin-1 levels were evaluated by ELISA. Variable data were compared by Mann Whitney U test and correlation was estimated by Spearman correlation analyses. The level of circulating netrin-1 protein was determined to be significantly lower in obese group compared to controls. The median value was 844 pg/mL in the control group and 338 pg/mL in the obese group ($p<0.0001$). Serum netrin-1 level was negatively correlated with HbA1c, LDL, cholesterol and triglyceride ($P< 0.01$). In addition, ROC curve analysis indicated that netrin-1 level could define the presence of obesity with AUC value of 0.8667 (95% Cl=0.7249-1.000; $P<0.0001$). Our study suggests that netrin-1 secretions are significantly reduced in obese subjects and negatively correlated with obesity markers. Therefore, netrin-1 can be evaluated as a possible potential biomarker for obesity.

**Keywords:** Obesity, Netrin-1, ELİSA, Biomarker.

**Öz:** Netrinler, hem nöral hem de vasküler gelişime rehberlik eden önemli sinyal proteinleridir. Netrin-1 hücre çoğalması, yapışması ve göçü gibi birçok fizyolojik süreci düzenler. Bu çalışmanın amacı obez bireylerde serum netrin-1 düzeyi ile biyokimyasal parametreler arasındaki ilişkiyi belirlemektir. Obez (n=15) ve kontrol (n=30) bireylerden serum örnekleri alındı. Serum netrin-1 seviyeleri ELISA ile değerlendirildi. Değişken veriler Mann Whitney U testi ile karşılaştırıldı ve korelasyon Spearman korelasyon analizleri ile belirlendi. Obez grupta serumda netrin-1 protein seviyesinin kontrollere göre anlamlı derecede düşük olduğu belirlendi. Ortanca değer kontrol grubunda 844 pg/mL ve obez grupta 338 pg/mL idi ($p<0,0001$). Serum netrin-1 düzeyi HbA1c, LDL, kolesterol ve trigliserit ile negatif korelasyon gösterdi ($P< 0,01$). Ayrıca, ROC eğrisi analizi, netrin-1 seviyesinin 0,8667 AUC değeri ile obezite varlığını tanımlayabildiğini gösterdi (%95 Cl=0,7249-1,000; $P<0,0001$). Çalışmamız, netrin-1 salınımının obez bireylerde önemli ölçüde azaldığını ve obezite belirteçleri ile negatif korele olduğunu göstermektedir. Bu nedenle netrin-1, obezite için olası bir potansiyel biyobelirteç olarak değerlendirilebilir.

**Anahtar Kelimeler:** Obezite, Netrin-1, ELİSA, Biyobelirteç.

*Corresponding author : Çiğdem AYDIN ACAR e-mail : cacar@mehmetakif.edu.tr
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## Introduction

Nutrition; it is the adequate intake of the nutrients required by our body in order to protect human health, improve the quality development. Today, modern life conditions cause excessive energy intake due to overnutrition, while finding solutions to health problems related to malnutrition (Cayir et al., 2011). The World Health Organization defines obesity as "the increase of fat cells to levels that adversely affect human health". Obesity is a public health problem that has become common



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in developed societies in recent years (Bakhshi et al., 2008). The age, gender, nutritional habits, sociocultural structure, daily physical activity and genetic structure of the individual play an active role in the diagnosis of obesity. It is very important to know the factors that cause obesity, to solve the health problems caused by obesity and to take pre-disease precautions (Deepa et al., 2009).

Netrin originates from the Sankrit word 'netr' and means 'guiding, leading' (Gorur et al., 2018). Netrins are a highly conserved family of proteins that direct axons to the ventral midline of the nervous system during embryogenesis (Rajasekharan and Kennedy, 2009). The first member of this family (UNC-6) was identified in a nematode, *Caenorhabditis elegans* (Yim et al., 2018). The gene organization was the first reported netrin UNC-5 (Rajasekharan and Kennedy, 2009). The first mammalian homologue of UNC-6 was discovered in 1994, and it has been reported to be a vital guide for the commissural axon found in the rodent spinal cord (Moore and Fisher, 2012). For mammals, five netrins are defined (netrin-1, -3, -4, -G1 and -G2). While netrin-1, netrin-3, netrin-4 are secreted from the membrane; netrin-G1 and netrin-G2 are membrane bound to the plasma membrane by two glycosylphosphatidylinositol (GPI) (Rajasekharan and Kennedy, 2009). Netrin has two identified receptors, DCC (deleted receptors in colorectal cancer) and UNC5 (uncoordinated 5). Netrin-1 is expressed in many tissues such as pancreas, lung, liver, intestines, spleen, kidney and vascular endothelial cells, especially in the central nervous system (Wang et al*.,* 1999).

The fact that netrin-1 receptors also have been identified in other cells in addition to neurons has strengthened the hypothesis that this protein may also have roles outside the central nervous system. Recent studies have revealed that netrin-1 is involved in many physiological processes from angiogenesis to inflammation (Rajasekharan and Kennedy, 2009).

In addition to its axonal guidance role in the central nervous system, new studies have shown that netrin also plays a role in cancer regulation. The upregulation of netrin-1 levels in tumors has brought up the possibility of being a biomarker that can be used in the early diagnosis of cancer. Recent studies have found strikingly increased levels of netrin-1 in blood samples from patients with kidney, liver, prostate, breast, menangioma, and glioblastoma (Mehlen and Furne, 2005; Ramesh et al., 2011). It has also been shown that netrin-1 plays a role in the development and formation of tissues other than nerve cells in cardiovascular and kidney diseases (Lu et al., 2004; Park et al., 2004; Ramesh, 2012; Wang et al., 2009).

In this study, it was aimed to determine the netrin-1 level in serum samples of obese subjects and to compare them with healthy controls, and accordingly to clarify the significant relationship between obesity and altered netrin-1 concentration.

## Materials and Methods

### Experimental design

Serum samples were obtained from obese (n=15) and control (n=30) groups. Human netrin-1 protein level in this samples was measured using ELISA (Enzyme-Linked Immuno Sorbent Assay). The determined netrin-1 concentrations were compared with the biochemical parameters (fasting blood glucose; HgA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance test; CRP, C-Reactive protein; HDL, high density lipoprotein; LDL, low density protein; TG, total triglyceride; TC, total cholesterol; TSH, thyroid stimulating hormone; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; sedimentation; creatinine) of the obese and control groups.

### Subjects

Blood samples were obtained from obese subjects and healthy controls who met the research criteria between August-2019-August-2021 in the Internal Medicine Clinic of Health Sciences University Antalya Training and Research Hospital (Antalya, Turkey). The demographic informations of



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patients were obtained by a trained clinician. Each test sample was recruited according to the inclusion and exclusion criteria. Inclusion criteria; BMI>30, absence of obesity-related chronic disease and exclusion criteria; presence of malignancy, presence of active infection, diabetes mellitus, peripheral vascular disease, atherosclerotic heart disease, hyperlipidemia, hypertension, kidney failure, smoking, BMI <30. This study was approved by the Health Sciences University Antalya Training and Research Hospital Clinical Research Ethics Committee [2019-215/04.07.2019]. All patients included in the study signed an informed consent.

**Blood collection and processing**

Whole blood samples were collected in serum vacuum tubes with clot activator and gel separator (BD Vacutainer). These samples were centrifuged for 10 minutes at 2500 x g to separate the serum. Finally, the obtained serum specimens were aliquoted and stored at -80 °C until experimental analysis.

**Detection of serum Netrin-1 levels by ELISA**

Serum netrin-1 levels were quantified in duplicate with specific Human Netrin-1 ELISA kit (#E1277Hu, Bioassay Technology Laboratory, Shanghai, China) according to the manufacturer's instructions. The minimum detectable human netrin-1 level was 10 pg/mL. After adding the stop solution in the final step, the optical density (OD) value of almost each test well was determined at 450 nm using a microplate reader (MultiscanGO, Thermo Fisher Sci.), Results were expressed as pg/mL.

**Statistical analysis**

Statistical analysis and graphical presentation were performed with Graph Pad Prism 9.0.2 software version. Data were expressed as median values or mean ± standart deviation. Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Mann Whitney U test was used for comparison of continuous variables. Correlation analyses were performed using the Spearman correlation test. ROC curve analysis was performed to determine the optimal cut-off values of serum netrin-1 with maximum specificity and sensitivity. p values < 0.05 were considered statistically significant.

**Results**

**Demographic and Biochemical Findings**

The obese group were consisted of 11 women (73%), 4 men (27%), and the control group were consisted of 23 women (77%), 7 men (23%). The mean age was 41.7 and 33.8 years in the obese and control groups, respectively.

By comparing the biochemical parameters of the obese and control groups, it was determined that HbA1c, CRP, LDL, TC and TG values were significantly higher in the obese group compared to the control group (p<0.0001, p:0.0002, p:0.0044, p:0.0299, p:0.0212, respectively). Fasting Insulin, HOMA-IR, Sedimentation, Creatinine, ALT, AST, HDL, BUN and TSH values were also compared between the obese and group, but no statistically significant difference was recorded (p:0.1034, p:0.1147, p:0.2404, p:0.3593, respectively). Demographic and biochemical findings of the obese and control groups are given in Table 1.

**Serum Netrin-1 Level in Obese and Control Groups**

Circulating netrin-1 levels of the obese and control groups were calculated and analyzed according to ELISA data. The minimum value was 224 pg/mL and the maximum value was 2274 pg/mL in the obese group, nevertheless the minimum value was 611.2 pg/mL and the maximum value was 4073 pg/mL in the control group. The median value of serum netrin-1 level was 338 pg/mL in the obese group, and 844 pg/mL in the control group. According to these results, serum netrin-1 level was statistically significantly decreased in the obese group compared to the control group (p<0.0001). The graphical representation of serum netrin-1 concentrations of the obese and control groups were shown in Figure 1.



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**Table 1.** Demographic and biochemical characteristics

| *Parameters* | *Obese Group (Mean)* | *Control Group (Mean)* | *P* |
|---|---|---|---|
| ***Age*** | 41,73 | 33,83 | **0,0376*** |
| ***Fasting insulin*** | 12,65 | 6,350 | 0,1034 |
| ***HbA1c*** | 6,050 | 5,204 | **<0,0001**** |
| ***HOMA-IR*** | 3,565 | 1,557 | 0,1147 |
| ***CRP*** | 11,94 | 1,220 | **0,0002***** |
| ***Sedimentation*** | 7,000 | 4,889 | 0,2404 |
| ***Creatinine*** | 0,7350 | 0,8000 | 0,3593 |
| ***ALT*** | 23,50 | 22,24 | 0,8097 |
| ***AST*** | 19,0 | 19,0 | 0,6233 |
| ***HDL*** | 58,77 | 65,90 | 0,1592 |
| ***LDL*** | 135,5 | 104,5 | **0,0044**** |
| ***TC*** | 222,0 | 189,8 | **0,0299*** |
| ***TG*** | 139,1 | 96,10 | **0,0212*** |
| ***BUN*** | 10,71 | 12,07 | 0,3472 |
| ***TSH*** | 1,947 | 2,192 | 0,5639 |

HgA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance test; CRP, C-Reactive protein; HDL, high density lipoprotein; LDL, low density protein; TG, triglyceride; TC, cholesterol; TSH, thyroid stimulating hormone; BUN, blood urea nitrogen; ALT, alain aminotransferase; AST, aspartate aminotransferase, *P<0.1;**P<0.01; ***P<.0.001; ****P<0.0001

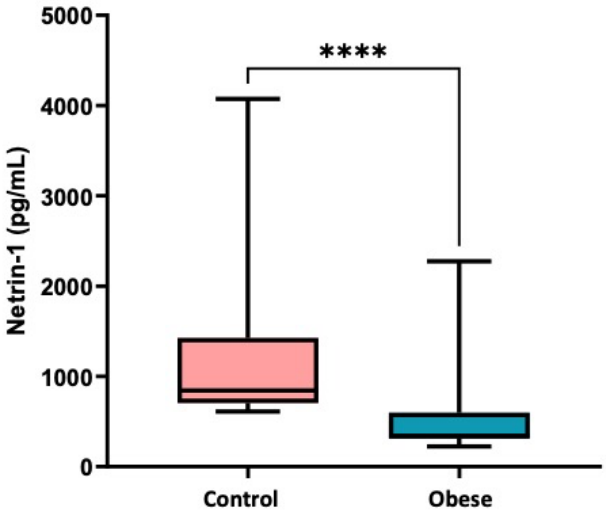


**Figure 1.** Distribution of serum netrin-1 level in obese and healthy control groups. Serum netrin-1 level was statistically significantly decreased in the obese group compared to the control group (p<0.0001). The center box and the middle line of each graph represent values from the bottom to the upper quartile (25th - 75th percentile) and the median, respectively. Horizontal lines represent the minimum and maximum values.



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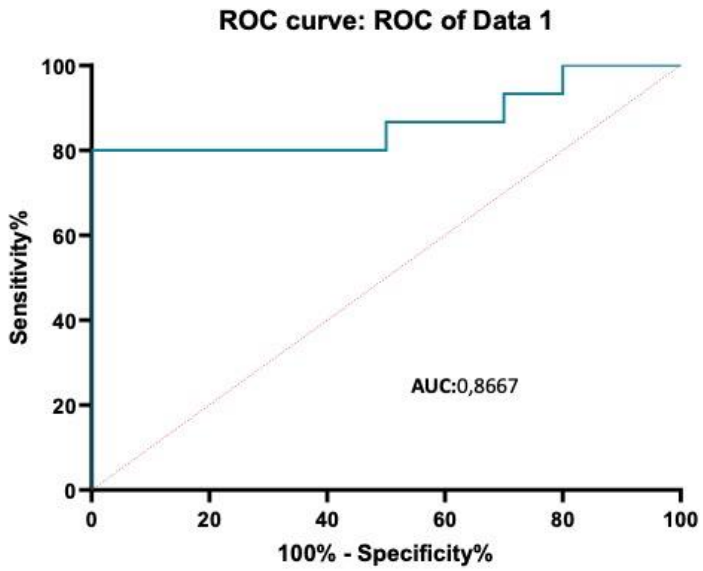


**Figure 2.** The Receiver Operating Characteristic (ROC) curve of serum levels of Netrin-1 to differentiate of obese from control. AUC: 0,8667 (95% Cl=0.7249-1.000; P<0.0001).

ROC curve analysis was used to measure of the usefulness and analyze diagnostic accuracy of the serum netrin-1 ELISA test that discriminate different two groups (Figure 2). The AUC (area under the ROC curve) was 0.8667 (95% Cl=0.7249-1,000; P<0.0001). The threshold value for serum netrin-1 was <624.2 pg/mL, with 80% sensitivity and 93.3% specificity in distinctive obesity.

**Serum Netrin-1 Level and Biochemical Parameters**

Spearman correlation was used to determine the association between serum netrin-1 level and biochemical parameters (Table 2). A negative correlation was found between serum netrin-1 level and HbA1c, LDL, TG (r= -5024; p: 0.0025, r=-0.3696; p: 0.0343, r=-0.3886; p: 0.0231). No significant correlation was determined between serum netrin-1 level and age, fasting insulin level, HOMA-IR, CRP, sedimentation, HDL, TC, TSH, BUN, ALT, AST and creatinine values.

**Discussion**

Obesity is an important worldwide public health problem that causes morbidity and needs novel therapeutic approaches and accepted international consensus for its treatment. It becomes very complicated with type 2 diabetes, liver diseases, cardiovascular diseases, hypertension, respiratory problems and some types of cancer (Mayoral et al., 2020).

Netrin is a family of highly conserved extracellular proteins with important roles in the central nervous system (Rajasekharan and Kennedy, 2009). Since the angiogenic, regenerative and anti-inflammatory properties of netrin-1 have been reported before, it was estimated that netrin-1 may be have important roles in various biological processes besides the central nervous system. In this context, the aim of this study is to reveal the potential association between obesity and netrin-1 concentrations.

A total of 45 volunteers, 15 of whom were obese and 30 were controls, were included in our study. Serum netrin-1 level was evaluated by ELISA method. In our study, it was clarified that serum netrin-1 level was statistically significantly lower in the obese group compared to the control group. In addition to these findings, a negative correlation was found between serum netrin-1 level and HgA1c, LDL, TG.



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**Table 2.** The correlation of serum netrin-1 and biochemical parameters of the obese and control groups.

| ***Variables*** | ***r*** | ***P*** |
|---|---|---|
| ***Age*** | -0,2916 | 0,0519 |
| ***Fasting insulin*** | -0,1752 | 0,5294 |
| ***HbA1c*** | -0,5024 | **0,0025**** |
| ***HOMA-IR*** | -0,2489 | 0,3495 |
| ***CRP*** | -0,4012 | 0,0642 |
| ***Sedimentation*** | -0,01583 | 0,9401 |
| ***Creatinine*** | 0,2517 | 0,1647 |
| ***ALT*** | 0,1868 | 0,2979 |
| ***AST*** | 0,1435 | 0,4411 |
| ***HDL*** | 0,2401 | 0,1784 |
| ***LDL*** | -0,3696 | **0,0343*** |
| ***TC*** | -0,2177 | 0,2236 |
| ***TG*** | -0,3886 | **0,0231*** |
| ***BUN*** | -0,03299 | 0,8841 |
| ***TSH*** | -0,1118 | 0,5101 |

HgA1c, glycosylated hemoglobin; HOMA-IR, insulin resistance test; CRP, C-Reactive protein; HDL, high density lipoprotein; LDL, low density protein; TG, triglyceride; TC, cholesterol; TSH, thyroid stimulating hormone; BUN, blood urea nitrogen; ALT, alain aminotransferase; AST, aspartate aminotransferase, *P<0.1;**P<0.01; ***P<.0.001; r= Spearman correlation coefficient.

Liu et al. (2016) evaluated plasma netrin-1 levels in newly diagnosed type 2 diabetes patients (n=30) and healthy controls (n=26). It was hereby determined that netrin-1 levels were significantly lower in patients with type 2 diabetes compared to the control group. This evidence was correlated with the results of our study. In this study, we reported that netrin-1 level was negatively correlated with HbA1c, HOMA-IR and fasting blood glucose levels. Although, the average level of HbA1c was recorded higher in obese individuals. In another study, it was reported that serum netrin-1 levels were significantly lower in the prediabetic group than in the control group. In that study, it was determined a negative correlation between serum netrin-1 levels and age, fasting blood glucose, HbA1c, CRP, and sedimentation data (Aydin Acar et al., 2021). Similarly, Nedeva et al. (2020) reported that serum netrin-1 levels were found to be significantly lower in obese, prediabetes and diabetes patient groups compared to the control group. In that study, a negative correlation was reported between BMI and serum netrin-1 levels. Briefly, netrin-1 was slightly increased in individuals with prediabetes. Therefore, it was shown that the netrin-1 levels could be affected by the amount of visceral adipose tissue mass. In correlation with HbA1c, the previous results are in accordance with each other. In this study, it has been suggested that netrin-1 may be involved in the formation of adipose tissue. In parallel with our findings, it was determined that the netrin-1 concentrations decreased in obese individual serum samples and



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increased while the BMI ratio was decreased (Nedeva et al., 2020).

Yim et al. (2018) compared serum netrin-1 levels between individuals diagnosed with type 2 diabetes or impaired blood glucose and a control group, and reported that the serum netrin-1 levels were significantly increased in patients group. Also, determined a positive correlation between serum netrin-1 level and HbA1c, fasting blood glucose, and HOMA-IR. Another recent study showed the elevated netrin-1 level in the urine were correlated significantly with insulin resistance in obese individuals diagnosed with kidney failure. A positive correlation of fasting insulin levels and HOMA-IR values with netrin-1 concentrations was also reported. As a result, it was stated that netrin-1 levels in the urine samples can be used as a biomarker for renal failure and insulin resistance in obese children (Ovunc Hamdioglu et al., 2016). In the previous study that carried out with diabetic individuals diagnosed with microalbuminuria, determined significant elevated netrin-1 expressions. Moreover, a positive correlation was found between netrin-1 and HbA1c values (Ay et al., 2016). The link between these two parameters needs to be further clarified, whether netrin-1 can be used as a biomarker for obesity. In line with our preliminary findings, this study hypothesizes that serum netrin-1 level can be used as a potential biomarker in the development of obesity.

In our study, the serum netrin-1 level was determined to be precisely lower in the obese group compared to the healthy control group. In addition, serum netrin-1 level was determined to be negatively correlated with HbA1c, LDL, TG. ROC analysis was performed to measure of the diagnostic ability, clinical sensitivity and specificity of the netrin-1 test to discriminate the two different groups. The AUC was calculated as 0.8667(95% Cl=0.7249-1,000; P<0.0001). An AUC of less than 0.5 is considered indiscriminate, with 0.5-0.6 bad, 0.7-0.8 good, 0.8-0.9 very good, and 0.9-1.0 defined as perfect. Since the range of this study was between 0.8 and 0.9, the serum netrin-1 ELISA method can be considered as a "very good" method in differentiating obese individuals from normal individuals. These results show that netrin-1 can be used as a biomarker in obesity. In our study, a threshold value of <624.2 pg/mL for serum netrin-1 was determined with 80% sensitivity and 93.3% specificity in detecting obesity.

In conclusion, our findings suggest that lower netrin-1 level is associated with obesity and may be a potential biomarker for obesity. However, it needs to be supported by further studies performed with different and larger groups. Meanwhile, we propose with our findings that netrin-1 will be evaluable in the creation of new therapeutic approaches for obesity in the future.

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## Conflict of interest

The authors declare that they have no conflicts of interest.

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