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Original Article

# Investigation of Serum Neprilysin Levels in Overweight and Normal Weight Young Women

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## ABSTRACT

***Background*** In this study we aimed to evaluate biochemical, lipid and glycemic parameters and to compare serum neprilysin levels between overweight (OW) and normal weight (NW) young women who are more prone to gain weight.

***Material and Methods*** A total of 28 overweight/obese women aged between 22-34 years and 34 age matched normal-weight women were included in this cross-sectional study on voluntary basis. of the subjects were performed, Participants' anthropometric measurements, hormone profiles, glycemic parameters and insulin resistance, and serum neprilysin levels were recorded and analyzed. Patients were evaluated in two groups as Group OW and Group NW.

***Results*** The mean ALT, TSH and uric acid values were statistically significantly higher in Group OW compared to Group NW (for all, $p<0.05$). The mean HDL-c was statistically significantly lower in Group OW than in Group NW ($p<0.01$), while the mean triglyceride level was significantly higher in Group OW than in Group NW ($p=0.002$). The mean fasting blood glucose, insulin, HOMA, HbA1c and triglyceride values were statistically significantly higher in Group OW compared to Group NW (for all, $p<0.001$). The mean neprilysin (NEP) value was found as 1123.44±1327.60 mmol/L in Group NW and 1229.39±1315.17 mmol/L in Group OW with no statistically significant difference between the groups. No significant correlation was found between NEP and BMI values.

***Conclusions*** In this study, no significant difference was found between serum neprilysin levels of overweight/obese and normal weight women, suggesting that neprilysin does not play a role in the pathogenesis of obesity, insulin resistance or diabetes.

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## Introduction

Obesity represents a significant global public health problem with health care and socio-economic impacts. The increasing number of owerweight and obese people has been described as epidemic and even pandemic in the last few decades.[1] The impact and prevalence of obesity are disproportionately higher in women than men and are rapidly increasing. According to the 2017 Health Survey for England, the prevalence of obesity in women increased from 15% in 1994 to 29% in 2017 (available at: https://files.digital.nhs.uk/EF/AB0F0C/HSE17-Adult-Child-BMI-rep-v2.pdf). Obesity in women increases the risk of developing comorbidities including endocrine, cardiovascular and musculoskeletal diseases, malignities, infertility and depression.[2] In addition, overweight and obesity are known to be closely linked with insulin resistance, resulting in increased risk of metabolic syndrome.[3] It has been reported that young women (18-36 years) gain weight at a higher rate than women in any other age group, although little is known about the determinant of weight gain in young women.[4]

Also known as neutral endopeptidase, enkephalinase or EC3 4.24.11, neprilysin (NEP) is an integral membrane zinc metalloendopeptidase widely expressed on the surface of a wide spectrum of cells ranging from pancreatic islet cells to non-pancreatic endothelial, epithelial and smooth muscle cells to, cardiac myocytes and fibroblasts.[5,6] NEP breakdowns peptides at the N-terminal side of hydrophobic amino-acid residues and play a role in the degradation and inactivation of various bioactive peptides, including angiotensins I and II, bradykinin, atrial natriuretic peptide, enkephalins and chemotactic peptides, some of which are known to modulate glucose metabolism.[7] It is also involved in the regulation of insulin receptor pathways in pancreatic β cells. On the other hand, NEP is also produced by adipocytes, suggesting the possibility of its potential role as an adipokine in the regulation of adipocyte function.[8] In association with obesity, NEP has been reported to directly contribute to the development of insulin resistance.[9,10] and to correlate with body mass index, cholesterol and triglycerides.[11] Patients with obesity or heart failure have been reported to have absolute or relative NEP deficiency, respectively.[12] In animal studies, NEP activity was increased in metabolic tissues and plasma of mice with diet-induced obesity and NEP levels were correlated with reduced insulin sensitivity and reduced β cell functioning.[13] However, the data are less clear in humans. Although there is some evidence that plasma levels of NEP are positively correlated with BMI and other characteristics of metabolic syndrome, this needs to be confirmed with additional studies.[6] Therefore, the objective of this study was to compare serum NEP levels in overweight and normal weight young women who are more prone to gain weight.

## Material and Methods

This cross-sectional study was conducted in the Department of Endocrinology and Metabolism of our hospital. Before the beginning of the study, ethics approval was obtained from the local ethics committee of our hospital. All participants were informed about the objective of the study in detail and gave informed verbal and written consent. The study was performed in line with the ethical principles of the Declaration of Helsinki.

A total of 28 overweight/obese volunteer women and 34 age matched normal-weight women were included in this cross-sectional study on voluntary basis between 2017 and 2019 Participants were divided into two groups as those with a body mass index (BMI) <25 kg/m$^2$ (Group NW) and subjects with a BMI ≥25 kg/m$^2$ (Group OW). After systemic examination and anthropometric measurements of the subjects were performed, participants' hormone profiles, glycemic parameters and insulin resistance, and serum neprilysin levels were recorded and analyzed. The variables studied included demographic features such as age, weight, height, BMI (dividing weight in kilos by height square in m$^2$), waist circumference, hip circumference, waist/hip ratio, waist/height ratio, fat percentage, systolic (SBP) and diastolic (DBP) blood pressures, pulse, fasting blood glucose, postprandial blood glucose, urea, creatinine, total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglycerides, insulin, c-peptide, homeostatic model assessment-insulin resistance (HOMA-

IR), oral glucose tolerance test (OGTT), aspartate transaminase (AST), alanine transaminase (ALT), st4, thyroid stimulating hormone (TSH), uric acid, glycosylated haemoglobin A1c (HbA1c), NEP and fibroblast growth factor-19 (FGF19) levels. Subjects with cardiovascular disease or previously diagnosed diabetes mellitus and those who rejected participation were excluded from the study.

All anthropometric measurements were made as previously described. The measurements were repeated twice and the average value was recorded. Fasting blood glucose samples were collected from all participants for analysis and lipid subfractions, glucose, insulin and hemostatic factors were measured as previously described.[6] SBP and DBP levels were measured in subjects with a sitting position twice and the averaged result was noted. OGGT was measured at $0^{th}$ and $2^{nd}$ hours after administering 75 g glucose. Soluble NEP in plasma samples was determined with a Solid Phase Sandwich ELISA (R&D Systems, Minneapolis, MN, USA) method.

*Statistical Analysis*

Normality of the variables was tested with the Kolmogorov-Smirnov method. Mann-Whitney U test was used for comparison of the continuous variables and Chi-square for comparison of the continuous variables between the groups. Continuous variables are expressed as mean±standard deviation descriptive statistics and categorical variables as frequency (number, percentage). Correlations between the variables were evaluated with Pearson's correlation analysis. $p<0.05$ values were considered statistically significant. All statistical analyses were performed using SPSS v. 23 (SPSS, Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) statistical software.

## Results

The mean age was 27.60±3.07 years in all participants, 27.74±2.85 years in Group NW and 27.43±3.36 years in Group OW. No statistically significant difference was found between the groups in terms of the mean age (p=0.960). The mean BMI value was found as 21.42±2.14 kg/m$^2$ in Group NW and 31.91±4.85 kg/m$^2$ in Group OW (p<0.001). Demographic features and anthropometric measurements of the subjects are given in Table 1.

In the biochemical analysis, the mean ALT, TSH and uric acid values were statistically significantly higher in Group OW compared to Group NW (for all, p<0.05). No statistically significant difference was found between the groups in terms of the other biochemical parameters. Biochemical parameters of the subjects are presented in Table 2.

**Table 1.** Demographic and anthropometric characteristics of the groups.

| | Group NW (mean±SD) | Group OW (mean±SD) | Total (mean±SD) | p value |
|---|---|---|---|---|
| Age (years) | 27.54±2.85 | 27.43±3.36 | 27.60±3.07 | 0.96 |
| Height (cm) | 163.41±5.72 | 162.82±6.26 | 163.15±5.93 | 0.46 |
| Weight (kg) | 57.06±5.04 | 84.51±12.4 | 69.46±16.48 | <0.001* |
| BMI (kg/m$^2$) | 21.42±2.14 | 31.92±4.85 | 26.16±6.38 | <0.001* |
| Waist circumference (cm) | 71.47±5.64 | 96.62±11.52 | 82.37±15.23 | <0.001* |
| Hip circumference (cm) | 96.76±4.74 | 112.08±8.2 | 103.40±9.98 | <0.001* |
| Waist/hip ratio | 0.74±0.05 | 0.86±0.07 | 0.79±0.08 | <0.001* |
| Waist/height ratio | 0.44±0.04 | 0.60±0.07 | 0.51±0.1 | <0.001* |
| Fat percentage (%) | 23.14±4.42 | 37.33±5.14 | 29.42±8.52 | <0.001* |

*Mann-Whitney U test.
BMI: body mass index, SD: standard deviation.

**Table 2.** Biochemical laboratory values of the subjects.

| | Group NW (mean±SD) | Group OW (mean±SD) | Total (mean±SD) | p value |
|---|---|---|---|---|
| SBP (mmHg) | 110.59±7.36 | 112.50±6.45 | 111.45±6.98 | 0.226 |
| DBP (mmHg) | 66.12±12.10 | 70.71±7.16 | 68.19±10.36 | 0.080 |
| Pulse (bpm) | 79.32±5.46 | 78.75±5.15 | 79.06±5.29 | 0.557 |
| Urea (mg/dL) | 21.88±5.61 | 21.19±4.40 | 21.57±5.08 | 0.827 |
| Creatinine (mg/dL) | 0.67±0.07 | 0.71±0.10 | 0.69±0.09 | 0.141 |
| AST (U/L) | 16.59±4.28 | 18.26±17.33 | 17.33±5.64 | 0.312 |
| ALT (U/L) | 13.56±7.72 | 21.41±14.64 | 17.03±11.88 | 0.003* |
| ST4 (ng/dL) | 1.16±0.20 | 1.15±0.14 | 1.16±0.17 | 0.420 |
| TSH (mIU/L) | 2.07±3.40 | 2.31±1.45 | 2.18±2.68 | 0.029* |
| Uric acid (mg/dL) | 3.29±0.84 | 4.06±0.72 | 3.59±0.87 | 0.002* |

*Mann-Whitney U test, p<0.05: statistically significant.
SBP: systolic blood pressure, DBP: diastolic blood pressure, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TSH: thyroid stimulating hormone, SD: standard deviation."

When lipid profiles of the subjects were examined; the mean HDL-c was statistically significantly lower in Group OW than in Group NW (p<0.01), while the mean triglyceride level was significantly higher in Group OW than in Group NW (p=0.002).

In the analysis of glycemic parameters; the mean fasting blood glucose, insulin, HOMA, HbA1c and triglyceride values were statistically significantly higher in Group OW compared to Group NW (for all, p<0.001). The mean HDL-c value was significantly lower in Group OW than in Group NW (p<0.05). No significant difference was found between both groups in terms of the other glycemic parameters (for all, p>0.05). Lipid and glycemic parameters of the subjects are presented in Table 3.

The mean OGTT result was found as 88.4±6.95 mg/dL in Group NW and 94.5±9.42 mg/dL in Group OW at the 0$^{th}$ hour with nos significant difference between the groups (p=0.300). The mean OGTT result was found as 97.6±19.13 mg/dL in Group NW and 102.75±24.31 mg/dL in Group OW at the 2$^{nd}$ hour with nos significant difference between the groups (p=0.650). The mean FGF19 value was found as 88.68±45.09 pg/mL in Group NW and 90.21±71.47 pg/mL in Group OW with no statistically significant difference between the groups (p=0.815). The mean NEP value was found as 1123.44±1327.60 mmol/L in Group NW and 1229.39±1315.17 mmol/L in Group OW with no statistically significant difference between the groups (p=0.916) (*Figure 1*).

Correlations between the studied variables were examined using Pearson's correlation analysis. Accordingly, BMI was significantly correlated with glycemic and lipid parameters, while no correlation was found between NEP and BMI values (p>0.05) (*Table 4*).

**Table 3.** Lipid and glycemic parameters of the groups.

| | Group NW (mean±SD) | Group OW (mean±SD) | Total (mean±SD) | p value |
|---|---|---|---|---|
| Fasting blood glucose (mg/dL) | 81.82±9.09 | 89.0±9.23 | 85.06±9.77 | 0.001* |
| Insulin (mIU/L) | 7.93±4.30 | 14.18±6.37 | 10.67±6.12 | <0.001* |
| C-peptide (mcg/L) | 1.94±0.77 | 2.44±0.91 | 2.11±0.85 | 0.083 |
| HOMA-IR | 1.61±0.97 | 3.13±1.52 | 2.28±1.45 | <0.001* |
| HbA1c (%) | 5.28±0.19 | 5.46±0.23 | 5.32±0.22 | 0.037* |
| Total cholesterol (mg/dL) | 170.29±40.0 | 188.73±29.97 | 178.28±36.89 | 0.096 |
| HDL-c (mg/dL) | 55.44±9.79 | 44.04±7.38 | 50.50±10.45 | <0.001* |
| LDL-c (mg/dL) | 103.0±28.88 | 116.81±27.53 | 108.98±28.90 | 0.083 |
| Triglycerides (mg/dL) | 81.26±27.70 | 129.77±67.59 | 102.28±54.34 | 0.002* |

*Mann-Whitney U test, p<0.05: statistically significant; HOMA: homeostatic model assessment; HbA1c: hemoglobin A1c test; HDL-c: high density lipoprotein-cholesterol; LDL-c: low density lipoprotein cholesterol SD: standard deviation.

**Table 4.** Correlation of NEP and BMI values with lipid and glycemic parameters.

| | BMI | | NEP | |
|---|---|---|---|---|
| | r | p | r | p |
| BMI (kg/m$^2$) | 1 | - | 0.058 | 0.656 |
| NEP (ng/mL) | 0.058 | 0.656 | 1 | - |
| Fasting blood glucose (mg/dL) | 0.315 | 0.013* | -0.083 | 0.523 |
| Insulin (mIU/L) | 0.631 | <0.001** | 0.039 | 0.776 |
| C-peptide (mcg/L) | 0.386 | 0.009** | -0.114 | 0.455 |
| HOMA-IR | 0.639 | <0.001** | -0.022 | 0.872 |
| HbA1c (%) | 0.393 | 0.022* | -0.085 | 0.631 |
| Total cholesterol (mg/dL) | 0.249 | 0.055 | -0.094 | 0.473 |
| HDL-c (mg/dL) | -0.589 | <0.001** | -0.081 | 0.54 |
| LDL-c (mg/dL) | 0.289 | 0.025* | -0.173 | 0.185 |
| Triglycerides (mg/dL) | 0.52 | <0.001** | -0.016 | 0.901 |

*Pearson's correlation analysis, *p<0.05: significant correlation; **p<0.001: strong correlation. NEP: neprilysin, BMI: body mass index, HOMA: homeostatic model assessment, HbA1c: hemoglobin A1c test, HDL-c: high density lipoprotein-cholesterol, LDL-c: low density lipoprotein cholesterol.

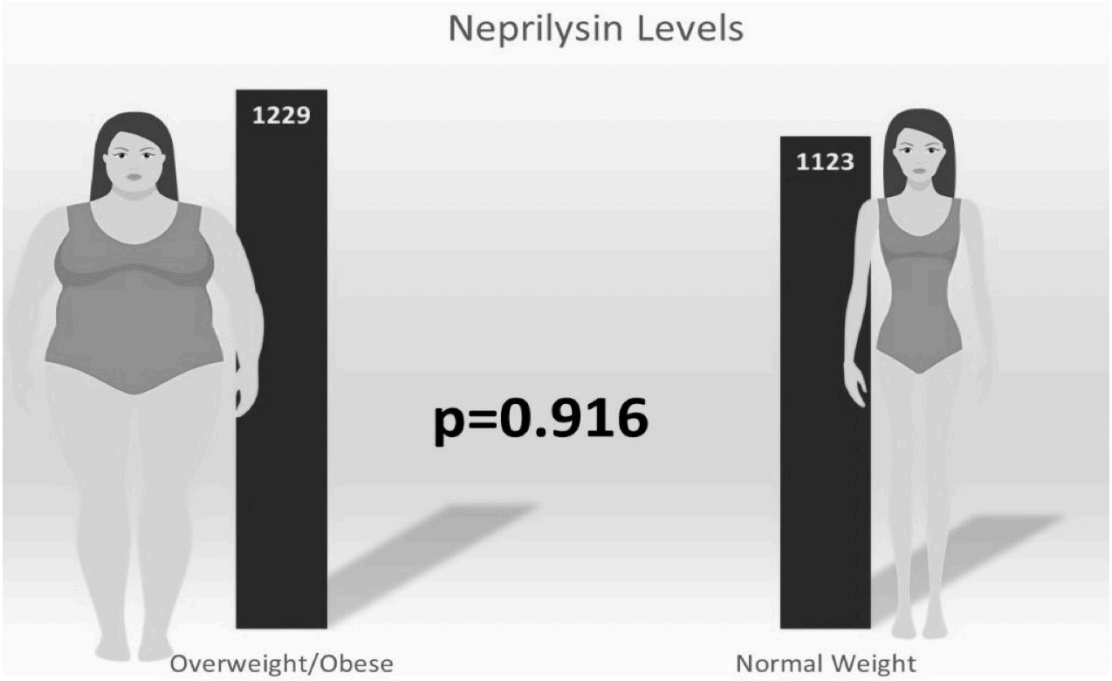


**Figure 1.** Comparison of neprilysin values between the overweight/obese and normal weight women.

## Discussion

The steadily increasing global prevalence of obesity especially among young women, and developed and developing countries, had led research to focus on the biological changes associated with the pathogenesis of obesity in relation to a wide range of comorbidities and medical conditions including insulin resistance and diabetes mellitus. As the primary outcome of this study, we could not find any association between NEP and obesity.

The impact and prevalence of obesity have a female predominance and also lead to substantial health care costs with women accounting for 31% higher obesity-related expenditure than men.[14] This has prompted researchers to study obesity from a wide perspective and especially in women.[1,2,14-16] In the present study, we compared overweight/obese and normal weight young women in terms of biochemical, lipid and glycemic parameters.

Young women between 18-36 years have been reported to gain weight at a higher rate than in women in any other age group.[4] In our study, the mean age was found as 27.43 years. Jönsson et al. reported the mean age of obese women in their study as 30.90 years.[17] In this context, the mean age of our participants was consistent with the range reported in the literature. In the present study, anthropometric values were significantly higher in the overweight/obese group as expected.

Several biochemical parameters have been associated with obesity. Abdominal fat accumulation may represent a strong predictor of increased liver enzymes including AST and ALT.[18] In addition, BMI values, which is the primary indicator of obesity, has been associated with elevated ALT in non-diabetic people.[19] Similarly, in the present study, the mean ALT value was significantly higher in the overweight/obese group.

Serum uric acid is an end product which is produced by endogenous metabolism and exogenous urine.[20] Duan et al.[21] reported that high serum uric acid was positively associated with obesity in overweight and obesity groups. This association has been reported also by numerous studies.[22,23] In our study, the mean uric acid level was significantly higher in the over weight/obese women.

The interactions between thyroid function, weight control and obesity have been well-established. Obese people with a normal thyroid gland tend to have higher serum TSH and thyroid hormones in serum due to the activation of hypothalamic-pituitary-thyroid axis.[24] In the

present study, the mean TSH value was found to be statistically significantly higher in overweight/obese participants (p=0.02). On the other hand, lipid and glycemic parameters were significantly different in overweight/obese group as expected since their relationships with BMI and obesity are well-known.

NEP metalloendopeptidase has been proposed to have a potential role as an adipokine in the regulation of adipocyte function is it is also secreted by adipocytes.[8] Studies on the association between NEP and obesity are mostly animal experimental studies and research in humans lacks in the literature. Inhibition of NEP in obese insulin-resistant rats has been reported to improve insulin-mediated glucose disposal.[9] Standeven et al.[6] showed that adipose tissue levels of NEP were increased in obese insulin-resistant mice. Based on this finding and as NEP protein production in human adipocytes increased during cell differentiation, NEP increases with obesity. In addition, they claimed a correlation between BMI and NEP levels. Unlike these studies, we found no significant difference in NEP levels beetween overweight/obese young women and no significant correlation between NEP and BMI values. Of course it is not easy to compare these results and in order to draw more informed conclusions, this issue should be subjected to further studies to be performed on human subjects.

*Study Limitations*

Major limitation of our study is the relatively small sample size and being conducted in a single centre. However, this study is the first in the literature to investigate NEP in obese women as a strength, and lack of human studies on this issue make our study guiding for future studies. We believe that the main finding of our study will shed light on the research regarding the controversy about the role of NEP in obesity, insulin resistance and diabetes.

## Conclusions

In this study, no significant difference was found between serum NEP levels of overweight/obese and normal weight women, suggesting that NEP does not play a role in the pathogenesis of obesity, insulin resistance or diabetes. However, further comprehensive studies are needed to support this finding.

***Acknowledgment***

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

***Conflict of interest***

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

***Authors' Contribution***

Study Conception: SC; Study Design: OOG, SC; Supervision: OOG, SC; Materials: OOG, SC; Data Collection and/or Processing: OOG, SC; Statistical Analysis and/or Data Interpretation: OOG, SC; Literature Review: OOG, SC; Manuscript Preparation: OOG, SC; Critical Review: OOG, SC.

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