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DECREASED NESFATIN-1 LEVEL IN OVERWEIGHT DEPRESSED PATIENTS

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SUMMARY

Background: *Nesfatin-1 (NF-1) is a parameter that has been shown to have an important potential in the modulation of the emotional state such as depression. The study focused to investigate the relationship between the plasma NF-1 level and depression.*

Subjects and methods: *Seventy-three patients who have a major depressive disorder (MDD) and 71 healthy individuals participated in the study. Plasma NF-1 was analyzed by Enzyme Linked Immunosorbent Assay (ELISA) and compared according to the groups.*

Results: *The mean NF-1 was lower in the patients with MDD than being in the healthy (p:0.019). Plasma NF-1 level was statistically significantly lower in the overweight MDD than in the non-overweight MDD (p:0.024). We observed a negative correlation between plasma NF-1 level and age (r:-0.178, p:0.033), BMI (r:-0.212, p:0.011), HAM-D scores (r:-0.185, p:0.026). However, there was no correlation for smoking status in both groups (r:0.095, p:0.259).*

Conclusion: *This study demonstrated the relationship between plasma NF-1 level and MDD as well as overweight. Therefore, NF-1 might be related to certain nervous system pathologies as well as adipose tissue in the body.*

Key words: *depression - nesfatin-1 - body mass index*

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INTRODUCTION

Major depressive disorder (MDD), the main mood disorder characterized by loss of pleasure and some other symptoms including significant weight or appetite changes, insomnia and loss of energy, etc (Mogi et al. 2017, Beekman & Spijker 2018). MDD is a highly destructive disorder that has prolonged attacks and high recurrence rates that leads to a severe loss of function or event suicide (Mogi et al. 2017, Beekman & Spijker 2018). The lifetime prevalence of MDD was reported to range between ten to twenty-five percent for women and five to twelve percent for men (Mogi et al. 2017, Beekman & Spijker 2018). There has been much research so far but its etiology remains unclear. We know that Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction is closely related to depression (de Kloet 2005). Patients with MDD usually display psychomotor retardation and have no energy to do daily activities of living. We already know energy homeostasis plays a crucial role in mood-disorders and it was suggested that depleted energy in the human body might be related to depression since the brain requires huge energy to pursue its function (Gardner & Boles 2008). In addition, some energy regulating endocrine hormone (including nesfatin-1 (NF-1)) dysfunction was reported to play a role in MDD (Ari et al. 2011, Bloem et al. 2012, Ishitobi et al. 2012).

NF-1 is a novel hormone that is derived from the nucleobindin2 (NUCB2). NF-1 is present in the hypothalamus playing a vital role in satiety and regulation of body energy through a leptin independent-receptor (Oh-I et al. 2006, Yosten & Samson 2009, Sahpolat & Ari 2017). The role of NF-1 in satiety can be summarized as the anorexigenic effect, regulation of feed, and appetite. Although there is a growing interest regarding NF-1's receptor which mediates its actions, it remains unclear. It was demonstrated that NF-1 is present at a high amount in the brain, especially the hypothalamus (Prinz et al. 2016). Besides its effects on energy metabolism, appetite and so body weight, it was shown to play important role in emotion and mood (Hofmann et al. 2013, Pałasz et al. 2012, Hofmann et al. 2015). In the literature, it was reported that plasma NF-1 level was altered in various forms of neuropsychiatric disorders such as anxiety, depression (Ari et al. 2011, Pałasz et al. 2012, Hofmann et al. 2015). Interestingly NF-1 level was reported to be regulated by feeding in animals that fasting decreases NF-1 level and vice versa (Stengel et al. 2009). However, we know that bodyweight is an important regulator of plasma NF-1 level (Hofmann et al. 2013).

The present study aimed to investigate the role of NF-1 in MDD patients with and without overweight compared to healthy individuals and also analyze whether depression severity is related to body mass or NF-1.

SUBJECTS AND METHODS

Study Design

The present cross-sectional study is designed and performed at the Psychiatry Clinic of Van Yüzüncü Yıl University, Dursun Odabas Hospital. We recruited 73 patients who have a major depressive disorder (MDD) and 71 healthy volunteers. We diagnosed MDD by using the Diagnostic-Statistical Manual of Mental-Health-Disorders (DSM-5) (American Psychiatric Association 2013) at the psychiatry clinic. Healthy volunteers were enrolled from the wellbeing clinic consecutively. MDD was divided into 2 groups (41 overweight and 32 non-overweight) based on BMI. Patients whose BMI was lower than 25 were enrolled in the non-overweight group and those with BMI greater than 25 were enrolled in the overweight group. Inclusion criteria covered the following: MDD and individuals aged between 18-65 years old. Individuals were excluded if they: use any substance including alcohol, have another mental illness, have chronic medical comorbidities such as hypertension, diabetes mellitus, coronary artery disease, epilepsy, or another severe neurological disorder, infection, pregnancy, and women in their menstrual cycle. Sociodemographic information such as occupation, sex, age, education, smoking status, height, and weight were tabulated. The Institutional Ethics Committee of Van Yuzuncu Yil University approved the present research. All participants have given written informed consent.

Blood Samples and Measurements

All participants underwent routine psychiatric examinations as well as physical and neurological examinations. The severity of depressive findings was evaluated using the Hamilton's Depression-Scale (HAM-D) (Hamilton 1960). All samples were collected on the same day with a psychiatric interview. Venous samples were gained in the starving time following 8 hours of fasting by 2 ml tubes with EDTA. Then, they were carefully and immediately transferred from blood collection tubes to centrifuges. They were immediately frozen and gently and timely rocked to compress the activity of the proteinase enzyme until the centrifugation stage. Plasma was obtained after centrifugation at 3,000 xg for 15 min (4°C). This separated part was maintained at -80°C until its analysis. NF-1 was analyzed by Enzyme-Linked ImmunoSorbent Assay (ELISA) kit.

Data Analysis

The analysis of data was done using the Number Cruncher software (NCSS) (NCSS, Kaysville, UT, USA). All the data were expressed as frequency, rate, mean, and standard deviation. We used the Shapiro-Wilk test and graphical examinations to analyze the normality. We used the Student's Test to assess normally distributed quantitative data and OneWay Analysis of Variance (ANOVA) and a Games-Howell pairwise comparison test for the comparisons among three or more groups. We used the Pearson-Chi-square to compare data and Pearson's correlation test to analyze correlations among the quantitative variables. The significance level was accepted as $p<0.05$.

RESULTS

The groups showed a similar sociodemographic characteristic as shown in Table 1 and 2. This study included 73 MDD patients with a mean age of 36.22±11.14 years and 71 healthy participants with a mean age of 33.25±11.65 years. No statistically significantly difference was seen in factors including age, sex, BMI, and smoking habits between groups.

Table 1. Comparison of the mean values of study variables of two groups

Variables	Depression (n:73)	Control (n:71)	Signifance	
Age (years)	36.22±11.14	33.25±11.65	t:-1.561	p:0.121
Sex (female/male)	57/16	51/20	χ^2:0.750	p:0.386
BMI (kg/m^2)	26.06±4.10	24.80±4.39	t:1.775	p:0.078
Smoking (+/-)	22/51	15/56	χ^2:1.530	p:0.216
HAM-D	21.37±7.13	4.19±1.70	*t:19.75*	*p:0.001**
Nesfatin-1 (ng/ml)	0.41±0.29	0.56±0.43	*t:-2.375*	*p:0.019**

BMI: Body Mass Index; HAM-D: Hamilton Depression Rating Scale; Student's t-test (t); Pearson's chi-square test (χ^2); *p<0.05

Table 2. Comparison of the mean values of study variables of three groups

Variables	Overweight depression (n:41)	Non-overweight depression (n:32)	Control (n:71)	Signifance	
Age (years)	37.97±9.98	33.97±12.37	33.25±11.65	F:2.350	p:0.100
Sex (female/male)	31/10	26/6	51/20	χ^2:1.056	p:0.590
BMI (kg/m^2)	29.01±2.79	22.27±1.64	24.80±4.39	*F:35.370*	*p:0.001**
Smoking (+/-)	9/32	13/19	15/56	χ^2:4.813	p:0.090
HAM-D	20.15±6.65	22.94±7.50	4.19±1.70	*F:203.581*	*p:0.001**
Nesfatin-1 (ng/ml)	0.36±0.19	0.48±0.37	0.56±0.43	*F:3.847*	*p:0.024**

BMI: Body Mass Index; HAM-D: Hamilton Depression Rating Scale; Pearson's chi-square test(χ^2); one-way ANOVA (F); *p<0.05

Table 3. Evaluation of relationships between nesfatin-1 and other parameters

Variables	Nesfatin-1	
	r	*p*
Age	-0.178	*0.033**
BMI	-0.212	*0.011**
Smoking	0.095	*0.259*
HAM-D	-0.185	*0.026**

BMI: Body Mass Index; HAM-D: Hamilton Depression Rating Scale; r: Pearson's correlation coefficient; *p<0.05

The mean plasma NF-1 level was 0.41±0.29 ng/mL in the MDD and 0.56±0.43 ng/ml in the controls. It was found that the mean plasma NF-1 was statistically significantly lower in the MDD patients than the healthy controls (p:0.019). The mean NF-1 was lower in the overweighted MDD (0.36±0.19 ng/mL) and non-overweighted MDD (0.48±0.37 ng/ml) than the healthy (0.56±0.43 ng/ml). It was also determined that the mean plasma NF-1 was statistically significantly lower in the overweight MDD patients compared to both the non-overweight MDD patients and healthy (p:0.024). We observed a negative relationship between NF-1 and age (r:-0.178, p:0.033), BMI (r:-0.212, p:0.011), HAM-D scores (r:-0.185, p:0.026). However, there was no correlation for NF-1 and smoking status in both groups (r:0.095, p:0.259).

DISCUSSION

MDD patients had statistically significantly lower plasma NF-1 than healthy, and that there was a negative correlation between the plasma NF-1 and the depression severity. To our best knowledge, it is the first research investigating plasma NF-1 levels in overweight MDD and its results will keep it a projection for physicians in terms of evaluating the weight factor together in these patients.

In the literature, there are controversial results regarding plasma NF-1 level and depression. Korucu et al. reported that plasma NF-1 was low in MDD with suicidal ideation than in the controls and that it may be appropriate to predict suicide risk in MDD, which is compatible with our study (Korucu et al. 2018). Dede et al. examined plasma NF-1 and apelin levels in MDD before and 3 months after antidepressant treatment (Dede et al. 2017). They reported that plasma NF-1 levels before treatment were not different between MDD and controls. Besides, there was no substantial change in plasma NF-1 levels 3 months after antidepressant treatment. A study by Ari et al. stated that plasma NF-1 level was found to be higher among patients with MDD than healthy subjects (Ari et al. 2011). Other studies found higher plasma NF-1 level in severe MDD than healthy ones (Algul & Ozcelik 2018). Xiao et al. also showed a positive correlation between plasma NF-1 level and the depression severity (Xiao et al. 2018). A recent study reported that the instantaneous blood NF-1 ratio was also linked to reported depression in a mixed-sex population (Xia et al. 2018).

Interestingly, recent studies showed a positive association between MDD and plasma NF-1 levels in women (Hofmann et al. 2013, Hofmann et al. 2015) but this was absent in men (Hofmann et al. 2015). Evidence that the peptide has gender-specific changes were also identified in a study of suicides linked to depression. NF-1-related mRNA expression was found to be higher in men, while women were lower than controls who died without a diagnosis of psychiatric disorder (Bloem et al. 2012). This gender-specific regulation needs to be considered, thus, the fact that depression is more common in women (Mogi et al. 2017, Kessler et al. 1993) and thereby our study sample consisted mainly of women may be the reason why plasma NF-1 levels showed lower in our study compared to other studies.

Several studies have shown that NF-1 interacts with hormones and peptides of the nervous system in the condition of depression. Priece et al revealed NF-1 inhibited neuropeptide-Y (NPY) neurons in the arcuate nucleus (Priece et al. 2008). NPY was claimed to modulate stress/mood by its antidepressant and anxiolytic property (Caberlotto et al. 1998, Domschke et al. 2010, Rotzinger et al. 2010). NF-1 may activate serotoninergic-stress-sensitive neurons of the raphenuclei (RN) and nor-adrenergic of the locus coeruleus (LC) and activate the HPA-axis (Yoshida et al. 2010). It is well-known that the LC and RN are also the keypoints of the serotonergic-noradrenergic brain signaling systems. Besides, the RN is the main source for innervetions in the serotonergic area of the brain. Serotonin, the main neuro-transmitter accused for sleep, energy, libido, cognitive functions are affected in MDD (Kranz et al. 2010). Novel studies reported that NF-1 might cause an alteration in anxiety levels by melanocortin-system (Oh-I et al. 2006). This is considered to result from its inhibition on the GABA (Rao et al. 2003). In addition to these effects, the melanocortin activation was also linked to depression (Chaki & Okubo 2007).

Our study showed that there was a negative correlation between plasma NF-1 levels and BMI. Weight gain and so obesity have been important issues for patients who have been receiving antipsychotics, antidepressants, and other psychotropic medications. Researches investigating the relationship between plasma NF-1 levels and BMI report conflicting results. There is evidence that NF-1 was lower in people with a higher BMI. A study conducted by Hofmann et al. suggested that no significant difference was detected in NUCB2/NF-1 between the fasting states in obese children (Anik et al. 2014). Some studies revealed a negative relationship between plasma NF-1 levels and BMI (Oh-I et al. 2006, Tsuchiya et al. 2010). While a positive relationship between NF-1 and BMI was shown as well (Ogiso et al. 2011). Similarly, NF-1 has been reported to be increased in obesity, they were decreased in anorexia nervosa patients (Hofmann et al. 2015).

CONCLUSION

This study has some unique features. It is the first research evaluating plasma NF-1 levels in overweight, DPs, and the number of subjects in the present study is higher than in other studies, with 73 DPs and 71 healthy controls. That said, there are also some limitations to the present study. One of these limitations is that there was no data on plasma NF-1 levels in overweight, DP. Also, we believe that the analysis of other parameters (such as ghrelin, leptin, TNF, IL-6) as well as plasma NF-1 level would better elucidate the complex relationship between them in depression.

We demonstrated the relationship between plasma NF-1 levels and DPs as well as BMI. Therefore, the plasma NF-1 levels might be related to certain nervous system pathologies as well as adipose tissue in the body. In addition, assessing NF-1 level in the context of other biomarkers (e.g., TNF, IL-6, ghrelin, leptin) which are altered in overweight and depressed people could help us to understand better the role of NF-1 in MDD population. We recommend further studies to investigate the temporal relationship between plasma NF-1 levels and depression, weight gain.

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Contribution of individual authors:

Gulsen Teksin & Musa Sahpolat: study design, first draft, statistical analysis.

Faruk Kurhan: study design, data collection, first draft.

Cem Sesliokuyucu & Huseyin Bayazit: study design, first draft.

All authors approval of the final version.

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