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ORIGINAL ARTICLE

The evaluation of Nesfatin-1 levels in patients with OSAS associated with metabolic syndrome

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Abstract
Purpose The association of obstructive sleep apnea syndrome (OSAS) and metabolic syndrome (MS) has been demonstrated in studies and in recent years; the effect of OSAS on insulin resistance independent of the level of obesity is being investigated. Nesfatin-1 is a newly defined 82 amino acid protein with a precursor molecule of NUCB2 (nucleobindin 2). Nesfatin-1 is not only essential in regulation of food ingestion but also important in regulation of some brain functions, autonomic regulation, stress, mental state, and paradoxical sleep. We aimed to evaluate the relationship between OSAS and MS and the MS dependent or independent effect of Nesfatin-1 on this relationship.
Methods Patients admitted with clinical signs of OSAS are included. Patients are divided into three groups based on Apnea-Hypopnea Index (AHI) on Polysomnography (PSG) as mild, moderate, and severe OSAS. A total of 59 patients were included the control patients. Several OSAS parameters and laboratory findings which are and are not MS dependent are compared. Nesfatin-1 levels are evaluated in all OSAS patients with and without MS.
Results There were significantly more males in all groups ($p = 0.007$). There was no significant difference between groups in terms of Nesfatin-1 levels. Nesfatin-1 levels were significantly lower in MS group compared to non-MS group ($p = 0.021$).
Conclusion Nesfatin-1 which is known to play a role in the pathophysiology of insulin resistance can be a beneficial target in developing new therapeutic targets for treatment of patients with obesity without any toxic effects in the future.

Keywords Obstructive sleep apnea syndrome · Metabolic syndrome · Nesfatin-1

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Introduction

OSAS is a syndrome characterized by repeated episodes of complete (apnea) or partial (hypopnea) upper respiratory tract obstruction and frequently associated with decrease in blood oxygen saturation [1]. The prevalence of OSAS was 2 % in females and 4 % in males. Apnea in adults is defined as complete absence of respiration for 10 s (apnea) or a decrease of 50 % in respiration for 10 s (hypopnea) [2]. Together with the symptoms, laboratory findings are also required to reach a diagnosis of OSAS. The gold standard in diagnosis is Polysomnography (PSG) [3]. The main constituents of MS are abdominal obesity, insulin resistance (IR), increased blood pressure, and lipid abnormalities. The prevalence of MS increases with age and body mass and also the prevalence changes in different populations evaluated [4].

OSAS is related to IR and other factors known to increase cardiovascular risk are HT, obesity, and diabetes. In obese patients with OSAS, the development of systemic arterial HT can be related to sympathetic activation, increased blood leptin levels, and IR [5]. The co-existence of OSAS with MS has been demonstrated in several studies; and in recent years, the effect of OSAS on insulin resistance independent of the level of obesity has been widely investigated [6].

Nesfatin-1 is a newly defined 82 amino acid protein with a precursor molecule of NUCB2 (nucleobindin 2). The 82 amino acid NUCB2 is a peptide derivative which is converted to Nesfatin-1 by prohormone convertase [7]. The expression of NUCB2 from hypothalamic paraventricular nucleus decreases in fasting and this suggests that endogenous nesfatin could play a role in physiological control of appetite [8]. Nesfatin-1 is not only essential in regulation of food ingestion but also it is known to play important roles in regulation of some brain functions, autonomic regulation, stress, mental state, and paradoxical sleep [9].

We aimed to evaluate the relationship between OSAS and MS and the MS dependent or independent effect of Nesfatin-1 on this relationship.

Materials and methods

This study consisted of OSAS patients. The definition of OSAS was based on a combination of clinical symptoms (i.e., daytime excessive sleepiness) and at least one round of a standard polysomnography. Congestive heart failure, liver disease, chronic renal disease, patients with overt thyroid dysfunction, patients with a diagnosis of type 1 or type 2 DM, patients with hypothyroidism and hyperthyroidism are excluded from the study. All patients underwent a polysomnographic evaluation by a Compumedics PSG device (44 channels, E series, Australia). Polysomnographic recordings included two electroencephalogram (EEG) channels (C3/A2 and O2/A1), two electrooculogram channels, one submental electromyogram channel, and one electrocardiography (ECG) channel. Ventilatory monitoring included recording of oronasal airflow (with an oronasal thermistor), hemoglobin oxygen saturation by pulse oximetry (oxygen saturation measured via a finger oximeter), and respiratory movement (with an inductive plethysmography) including chest, abdomen, and body position. Sleep staging was performed according to the standard criteria of Retchschaffen and Kales guidelines and ASDA (American Sleep Disorders Association).

A total of 59 patients, 41 males and 18 females, aged between 18 and 72 years were included in this study. Patients were divided into 3 groups based on ASDA criteria AHI values as mild (AHİ 5–15), moderate (AHİ 15–30), and severe (AHİ ≥30) OSAS (Table 1). Male gender was more prevalent in all patient groups ($p = 0.007$). The demographic features and PSG findings of all patients in different groups in the study are shown in Table 2.

Table 1 Gender distribution according to OSAS classification and the relationships

OSAS	Gender		Total
	Male	Female	
Control	7	11	18
Mild	11	1	12
Moderate	10	2	12
Severe	13	4	17
Total	41	18	59

χ^2 p value = 0.007

There was a statistically significant difference between groups in terms of weight, height, waist circumference, BMI, SBP, DBP, total cholesterol, LDL-cholesterol levels. There was no significant difference between groups in terms of nesfatin-1. This difference between groups is shown in the following tables by alphabetical designation. There was no difference in the means of the groups with same letters; there was a significant difference between the groups designated with different letters (Table 3).

Definition of MS

ATP III criteria were taken as a reference for Metabolic Syndrome criteria [10]. Those patients who have at least 3 of these criteria were accepted as MS. The age, gender, and anthropometric measurements were recorded for all patients.

Blood samples

Fasting blood glucose level measurements were made at 0 and 2 h by 75 g oral glucose tolerance test and patients were shown not to have diabetes, at the same time, insulin levels were also measured at 0 and 2 h. Serum glucose, urea, creatinine, ALT, AST, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, insulin, 25-OH Vitamin D3, cortisol, Thyroid Stimulating Hormone (TSH) levels were also measured. A 1 mg dexamethasone suppression test was performed in order to exclude a diagnosis of Cushing's syndrome [11]. Insulin resistance and secretion were evaluated by Homeostatic Model Assessment (HOMA-IR) and Homeostasis model assessment β-cell (HOMA-β cell) HOMA β-cell formulas.

Table 2 The demographic features and PSG findings in different groups

	Control		Mild		Moderate		Severe		*p* value
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	
Age (years)	37.78	12.68	48.50	15.10	47.75	9.37	45.12	10.28	0.060
Height (cm)	167.94	10.14	173.25	9.13	169.50	7.59	170.47	7.953	0.453
Weight (kg)	90.00	13.56	93.75	15.13	83.83	9.15	103.44	24.90	**0.025**
Waist circ. (cm)	104.33	9.01	108.33	10.61	101.25	9.50	116.00	17.46	**0.011**
Neck circ. (cm)	37.77	3.93	40.16	3.18	38.75	2.45	40.17	4.12	0.178
BMI (kg/m^2)	32.16	5.95	31.19	4.15	29.20	3.14	35.63	8.04	**0.038**
SBP (mm/hg)	123.33	16.44	132.08	12.33	130.41	13.22	138.23	10.14	**0.018**
DBP (mm/Hg)	76.94	12.02	82.50	9.88	79.58	9.15	88.52	6.55	**0.007**
OGTT mg/dl-0 min	101.66	10.57	96.16	5.73	97.91	8.41	104.94	13.82	0.126
OGTT mg/dl 120 min	120.72	35.76	125.33	46.07	121.17	43.73	126.05	34.90	0.973
Ins mU/ml-0 min	41.00	7.99	40.25	8.40	36.83	7.30	37.52	7.69	0.403
Ins mU/ml-120 min	42.98	36.68	55.86	74.28	61.21	51.78	53.05	56.09	0.825
Cortisol (mg/dl)	16.20	6.65	14.73	4.59	14.98	5.98	11.65	3.80	0.100
T. cholesterol (mg/dl)	172.72	40.24	211.41	17.93	206.03	34.94	180.29	32.25	**0.006**
TG (mg/dl)	139.44	56.58	174.75	59.13	175.16	89.54	164.82	69.01	0.424
LDL (mg/dl)	104.85	34.80	135.75	19.74	128.75	32.38	109.44	26.64	**0.018**
25(OH)D3 (nmol/l)	41.66	25.51	36.87	13.89	40.05	14.39	41.71	14.42	0.894
TSH (IU/ml)	1.78	0.70	1.90	1.16	2.41	1.76	2.02	1.19	0.573
Nesfatin (pg/ml)	4.40	1.74	4.50	2.20	4.85	1.50	4.04	1.37	0.658
Apne-hipopne ind	1.58	1.19	10.65	2.62	23.48	4.20	61.00	20.70	**0.001**
REM % (min)	14.87	7.90	13.40	9.37	9.96	5.68	12.02	6.66	0.351
Stage 1 (min)	10.72	7.79	13.82	8.45	10.52	6.54	9.98	12.16	0.711
Stage 2 (min)	56.59	12.40	58.93	12.03	66.49	10.63	63.55	13.42	0.137
Stage 3 (min)	15.57	6.79	13.95	7.36	12.95	4.97	14.43	12.34	0.872
Arou-ind	15.35	4.76	17.81	12.75	24.95	10.49	28.48	21.41	**0.043**
EN-SO2	88.85	3.14	85.10	12.21	91.00	5.52	85.17	7.82	0.125
Tot-sleep (min)	412.33	46.52	384.95	68.73	384.41	99.34	318.94	138.81	**0.042**
Desat-ind	1.01	1.13	8.20	6.61	20.18	8.84	42.80	28.02	**0.001**

Bold values indicate statistical significance ($p < 0.05$)

Nesfatin-1

The quantitative measurement of Nesfatin-1 parameter was performed by enzyme-linked immunosorbent assay (ELISA) method. An optical density concentration graphic was constituted for Nesfatin-1 and the values for all samples were calculated with use of this graphic.

Statistical analysis

The SPSS v 17.0 for Windows statistical software package was used for statistical analysis of the findings. The normality of the numerical data was analyzed by Kolmogorov–Smirnov test. One-way analysis of variance (one-way ANOVA) was used in comparison of the 4 groups. Different groups were analyzed by Tukey's post-hoc test or Dunn's test and Student *T* test was used in 2 group comparisons. The comparison of groups in terms of categorical features was performed with χ^2 test. The relationships between variables were evaluated with Pearson's correlation.

Results

There was a statistically significant difference between the groups in terms of PSG findings of arousal index, total sleep time, desaturation index (p values $p = 0.043$, $p = 0.042$, $p = 0.00$, respectively). This difference between groups has been shown in the tables by giving specific letters. There

Table 3 Comparison of demographic features between groups

	Mean	Letter
Weight (kg)		
Severe	103.441	A
Moderate	83.83	B
Mild	93.750	Ab
Control	90.00	Ab
Waist circumference (cm)		
Severe	116.00	A
Moderate	101.25	B
Mild	108.333	Ab
Control	104.33	B
BMI (kg/m^2)		
Severe	35.63	A
Moderate	29.20	B
Mild	31.19	Ab
Control	32.16	Ab
SBP (mm Hg)		
Severe	138.23	A
Moderate	130.41	Ab
Mild	132.08	Ab
Control	123.33	B
DBP (mm Hg)		
Severe	88.52	A
Moderate	79.58	B
Mild	82.50	Ab
Control	76.94	B

Table 4 Comparison of PSG findings between groups

	Mean	Letter
Arou-index		
Severe	28.48	A
Moderate	24.95	Ab
Mild	17.81	Ab
Control	14.35	B
Total sleep time (min)		
Severe	318.94	B
Moderate	384.41	Ab
Mild	384.95	Ab
Control	412.33	A
Desaturation index		
Severe	42.80	A
Moderate	20.18	B
Mild	8.20	C
Control	1.01	C

was no difference in means of groups named with the same letters; there was a difference between groups of different letters (Table 4).

According to NCEP ATP III criteria, a diagnosis of MS was given to 33 (21 males and 12 females) patients. No significant differences between MS and OSAS groups were observed ($p = 0.052$) (Table 5). The demographic features of MS and Non-MS Patients are shown in Table 6.

When the two groups are compared, it was observed that the prevalence of MS increases with age ($p = 0.046$). In MS group, weight, BMI, waist circumference, neck circumference, SBP, and DBP values were significantly higher (p values are $p = 0.031$, $p = 0.001$, $p = 0.002$, $p = 0.044$, $p = 0.002$, and $p = 0.001$, respectively). The fasting plasma glucose levels were higher in MS group although not statistically significant; the plasma glucose levels after OGTT at 2 h were significantly higher in the MS group. Both basal and second hour insulin levels were significantly higher in the MS group ($p = 0.037$ and $p = 0.01$, respectively). The TG levels were significantly higher in MS group ($p = 0.001$). The Nesfatin levels in the MS group were significantly lower compared to non-MS group (4,981 ± 1,849 3,971 ± 1,427, $p = 0.021$). HOMA-IR and HOMA-β cell levels were higher in MS group although not statistically significant.

Discussion

OSAS is a syndrome characterized by hypoxia/reoxygenation and arousals, resulting from repeated episodes of complete or partial upper respiratory tract obstruction. In advanced ages (≥65), OSAS is a highly prevalent disorder [12]. In moderate age group males the frequency of OSAS was higher in females. In our study, the mean age of the total sample population was 44, 10 ± 12, 48 years and the frequency of male gender was significantly higher in all groups, which was in line with the literature data. Although there is no robust data to explain the gender related increase in OSAS prevalence, some efforts have been made to explain this with occupational and environmental factors, the structure of upper respiratory tract and the distribution of fat tissue [13].

Epidemiological studies have shown that obesity is an important risk factor for the development of OSAS. The prevalence of OSAS was 2 % in females and 4 % in males, while 30 % in obese and 50–98 % in morbidly obese subjects (kaynak 14 [14]). Obesity, especially increased fat tissue in the neck, leads to narrowing of the upper airway structure, alteration in its function (such as collapsibility), reductions in functional residual capacity and hypoxemia gain, and eventually the development of OSAS [15].

In our study, as is in the literature, the mean prevalence of MS in OSAS cases was 58 % with the prevalence rates of 50 and 82 % in mild and severe OSAS cases, respectively. The risk was even higher in morbidly obese patients [16].

Especially in severe OSAS cases, weight, waist circumference, BMI, and neck circumference values were higher compared to other groups. In high-AHI-valued OSAS patients, the higher existence of IR was demonstrated by higher fasting insulin levels, and these patients were also found to be older and more obese, and thus, it was proposed that every added apnea or hypopnea per one sleep hour increased fasting insulin levels and HOMA-IR by 5 % [17].

Table 5 The relationship between OSAS and MS

OSAS	Met-Send		Total
	No	Yes	
Control	9	9	18
Mild	6	6	12
Moderate	8	4	12
Severe	3	14	17
Total	26	33	59

χ^2 p value = 0.052

Hypothalamus is the main center of body weight energy balance. Nesfatin-1 was first described in 2006 as a satiety molecule secreted from the hypothalamus [18]. In the studies conducted, the antihyperglycemic effect of Nesfatin-1 as demonstrated by the secretory proteins that play a role in metabolic control in addition to its anorexia genic effects of it [19]. This appetite controlling effect was found to be independent of many transmitter systems but it was also demonstrated that it was associated with the melanocortin system [20]. Serum levels of Nesfatin-1 were found to be significantly lower in obese children than those of the control subjects [21].

In our study, significantly lower levels of Nesfatin-1 were detected in MS patients compared to non-MS patients which is in line with the previous literature findings. This indicates that Nesfatin-1 may serve as a link between obesity and OSAS. However, the exact mechanism needs to be explored by further studies.

It has been demonstrated that the administration of Nesfatin-1 after head trauma could significantly suppress gene expressions of nuclear factor kappa-B, lessen concentrations of tumor necrosis factor-alpha, interleukin-1β,

Table 6 The demographic features of MS and Non-MS Patients

	Non-MS		MS		p value
	Mean	Standard deviation	Mean	Standard deviation	
Age (years)	40.46	12.19	46.97	12.12	**0.046**
Height (cm)	172.84	8.45	167.87	8.62	**0.031**
Weight (kg)	87.84	13.90	97.74	20.35	**0.039**
Waist circ. (cm)	101.84	10.68	112.63	13.49	**0.002**
Neck circ. (cm)	38.07	3.75	40.00	3.41	**0.044**
BMI (kg/m^2)	29.33	3.70	34.75	6.81	**0.001**
SBP (mm/hg)	124.42	12.98	135.90	13.31	**0.002**
DBP (mm/hg)	75.57	9.93	86.97	7.99	**0.001**
OGTT mg/dl-0 min	97.84	8.17	103.00	12.12	0.068
OGTT mg/dl 120 min	102.23	30.60	139.87	36.20	**0.001**
Ins mU/ml-0 Min	85.61	8.75	89.81	5.48	**0.037**
Ins mU/ml-120 min	32.40	29.55	67.81	62.75	**0.010**
Cortisol (mg/dl)	13.84	5.46	14.98	5.69	0.438
BUN (mg/dl)	29.57	7.66	34.05	15.59	0.185
Creatinine (mg/dl)	0.86	0.15	0.90	0.28	0.553
AST (IU/ml)	23.03	5.82	29.51	23.09	0.169
ALT (IU/ml)	24.46	13.67	32.21	24.27	0.151
Total cholesterol (mg/dl)	181.34	40.46	196.03	31.95	0.125
TG (mg/dl)	127.46	50.11	187.78	69.57	**0.001**
LDL-C (mg/dl)	114.34	32.50	119.66	30.84	0.523
25(OH)D3 (nmol/l)	40.84	17.10	40.01	19.10	0.864
PRL (ng/ml)	8.73	4.70	7.61	4.90	0.381
TSH (IU/ml)	2.24	1.16	1.82	1.21	0.182
Nesfatin-1 (pg/ml)	4.98	1.84	3.97	1.42	**0.021**
Homa-IR	2.69	2.56	3.57	2.88	0.231
Homa-β cell	120.89	141.84	131.05	99.43	**0.**748

Bold values indicate statistical significance ($p < 0.05$)

and interleukin-6 in traumatic rat brain tissues [22]. Bonnet et al. [23] reported that a portion of Nesfatin-1 neurons of both the hypothalamus and brainstem are increased by the peripheral inflammatory stimulus of lipopolysaccharides. These results indicate the important role of Nesfatin-1 in the process of anti-inflammation. Inflammation is involved in the pathogenesis of OSAS. Therefore, Nesfatin-1 may be involved in the mechanism of OSAS through inflammatory pathway. The current results showed that serum Nesfatin-1 levels were significantly decreased in OSAS patients compared with healthy controls; and serum Nesfatin-1 levels in severe OSAS patients were significantly reduced compared with those in mild and moderate OSAS [24]. This indicates that Nesfatin-1 may be involved in the pathophysiology of OSAS. Decreased levels of serum Nesfatin-1 could serve as a new biomarker to predict the presence of OSAS. In our study, there was no significant difference between groups in terms of Nesfatin-1 levels. Although the patients included in our study were grouped based on their AHI values, they are selected randomly based on their anthropometric measurements.

Paradoxical sleep (REM) is the stage of the sleep where muscle tonus is lost and shaking of the legs can sometimes be observed. The paradoxical sleep in adults occurs cyclically and constitutes 20–25 % of a normal whole night's sleep. In their study on rats, Jego et al. [9] observed a positive correlation between Nesfatin-1 levels and paradoxical sleep and supporting this observation they showed a decrease in paradoxical sleep episodes in the rats given anti Nesfatin-1 serum. In contrary to these findings of Jego et al. in our study, we have observed a negative correlation between Nesfatin-1 and REM. This can be due to the fact that the patients in our study were selected randomly in terms of anthropometrical and demographical measurements. On the other hand, another reason for this conflicting result can be explained by the inherent nature of the study byJego et al. that is an animal study.

Another study on rats found similar findings to our results which demonstrated a negative feedback effect of Nesfatin-1 to REM [25]. Existence of depression and anxiety was reported in 30 % of OSAS cases [26]. In a study on patients with panic disorders and anxiety, the mean plasma Nesfatin-1 levels were found to be higher compared to controls [27]. In our study although the degree of BMI, obesity was found to be increased with the severity of OSAS, Nesfatin-1 levels were not significantly lower. In the light of the literature data, this situation can explain why Nesfatin-1 levels were lower than it was expected in situations of depressive mood and anxiety where it normally tends to increase.

Conclusion

OSAS is a risk factor for MS. MS should definitely be investigated and treated in patients with OSAS, and sleep disorders should be investigated in patients with MS. Nesfatin-1 which is known to play a role in the pathophysiology of IR and OSAS seems to play a role in finding a non-toxic pharmacological target in developing new treatment options for obese patients. All the studies on the detailed evaluation of the relationship between energy balance-metabolism- Nesfatin-1 triad will make positive contributions in the fight against obesity and other obesity related co-morbidities. Nesfatin-1 may be involved in the pathophysiology of OSAS. Decreased levels of serum Nesfatin-1 could serve as a new biomarker to predict the presence of OSAS.

Conflict of interest The authors declare they have no conflict of interest.

References

1. American Academy of Sleep Medicine (2005) ICSD-2: the international classification of sleep disorders. diagnostic and coding manual, 2nd edn, Westchester, Illinois
2. Susheel PP, Hartmut S, Alan RS et al (2007) Adult obstructive sleep apnea-pathophysiology and diagnosis. Chest 132:325–337
3. Olson LG, Ching MT, Hensley MJ, Saunders NA (1995) A community study of snoring and sleep-disordered breathing. Prevalence. Am J Respir Crit Care Med 152:711–716
4. Fulop T, Tessier D, Carpentier A (2006) The metabolic syndrome. Pathol Biol (Paris) 54:375–386
5. Tiengo A, Fadini GP, Avogaro A (2008) The metabolic syndrome, diabetes and lung dysfunction. Diabetes Metab 34:447–454
6. Xu E, Schwab M, Marette A (2013) Role of protein tyrosine phosphatases in the modulation of insulin signaling and their implication in the pathogenesis of obesity-linked insulin resistance. Rev Endocr Metab Disord 14:79–97
7. Oh-I S, Shimizu H, Satoh T et al (2006) Identification of Nesfatin-1 as a satiety molecule in the hypothalamus. Nature 12(443):709–712
8. Su Y, Zhang J, Tang Y, Bi F, Liu JN (2010) The novel function of nesfatin-1: antihyperglycemia. Biochem Biophys Res Commun 39:1039–1042
9. Jego S, Salvert D, Renouard L et al (2012) Tuberal hypothalamic neurons secreting the satiety molecule Nesfatin-1 are critically involved in paradoxical (REM) sleep homeostasis. PLoS ONE 7:52525
10. Grundy SM, Cleeman JI, Daniels SR et al (2005) Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Insitute Scientific Statement. Circulation 112:2735–2752
11. Lindholm J (2013) Cushing's disease, pseudo-Cushing states and the dexamethasone test: a historical and critical review. Pituitary 17(4):374–380
12. Partinen M, McNicholas T (1998) Epidemiology, morbidity and mModeratelity of the sleep apnoea syndrome. Eur Respir Monograph 10:63–74

13. Yılmaz M, Bayazit YA, Ciftci TU et al (2005) Association of serotonin transporter gene polymorphism with obstructive sleep apnea syndrome. Laryngoscope 115:832–836
14. Soylu AC, Levent E, Sarıman N, Yurtlu S, Alparslan S, Saygı A (2012) Obstructive sleep apnea syndrome and anthropometric obesity indexes. Sleep Breath 16:1151–1158
15. Tuomilehto H, Seppä J, Uusitupa M (2013) Obesity and obstructive sleep apnea—clinical significance of weight loss. Sleep Med Rev 17:321–329
16. Schwab RJ, Goldberg AN, Pack AL (1998) Sleep apnea syndromes. In: Fishman AP (ed) Fishman' s pulmonary diseases and disorders. McGraw Hill Book Company, New York, pp 1617–1637
17. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS (2002) Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 165:670–676
18. Shimizu H, Oh-I S, Hashimoto K et al (2009) Peripheral administration of Nesfatin-1 reduces food intake in mice: the leptin-independent mechanism. Endocrinology 150:662–671
19. Su Y, Zhang J, Tang Y et al (2010) The novel function of nesfatin-1: anti-hyperglycemia. Biochem Biophys Res Commun 391:1039–1042
20. Cui H, Sohn JW, Gautron L et al (2012) Neuroanatomy of melanocortin-4 receptor pathway in the lateral hypothalamic area. J Comp Neurol 520:4168–4183
21. Abaci A, Catli G, Anik A, Kume T, Bober E (2013) The relation of serum Nesfatin-1 level with metabolic and clinical parameters in obese and healthy children. Pediatr Diabetes 14:189–195
22. Tang CH, Fu XJ, Xu XL, Wei XJ, Pan HS (2012) The anti-inflammatory and anti-apoptotic effects of Nesfatin-1 in the traumatic rat brain. Peptides 36:39–45
23. Pecchi E, Bonnet MS, Trouslard J, Jean A, Troadec JD, Dallaporta M (2009) Central nesfatin-1-expressing neurons are sensitive to peripheral inflammatory stimulus. J Neuroinflammation 6:27
24. Shen P, Han Y, Cai B, Wang Y (2014) Decreased levels of serum Nesfatin-1 in patients with obstructive sleep apnea syndrome. Sleep Breath. doi:10.1007/s11325-014-1039-0
25. Vas S, Ádori C, Könczöl K et al (2013) Nesfatin-1/NUCB2 as a potential new element of sleep regulation in rats. PLoS ONE 8:59809
26. Fletcher EC (2000) Cardiovascular consequences of obstructive sleep apnea: experimental hypoxia and sympathetic activity. Sleep 23:127–131
27. Bez Y, Ari M, Ozturk OH, Oktar S, Can Y, Sogut S (2010) Plasma Nesfatin-1 level may be associated with disease severity in patients with panic disorder. BCP 20:288–292