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Diagnostic and prognostic value of Nesfatin-1 in sepsis and septic shock

İlkim Deniz TOPRAK[1], Hasan ERUZUN[2,*], Yasin KUTLU[3], Yücel ARMAN[4] Pembegül YUMUŞTUTAN[5], Şengül AYDIN YOLDEMİR[4], Murat AKARSU[4], Okan DİKKER[6], Tufan TÜKEK[7]

[1]Department of Internal Medicine, Faculty of Medicine, University of Health Sciences Gaziosmanpasa Taksim Training and Research Hospital, Istanbul, Turkey
[2]Department of Gastroenterology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[3]Department of Medical Oncology, Faculty of Medicine, Medipol University, Istanbul, Turkey
[4]Department of Internal Medicine, Prof. Dr. Cemil Taşçıoğlu City Hospital, Istanbul, Turkey
[5]Department of Internal Medicine, Uskudar Public Hospital, Istanbul, Turkey
[6]Department of Medical Biochemistry, Prof. Dr. Cemil Taşçıoğlu City Hospital, Istanbul, Turkey
[7]Department of Internal Medicine, Faculty of Medicine, Istanbul University, Istanbul, Turkey

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Abstract

Nesfatin-1 is an anorectic protein, and we expect it to decrease during sepsis and septic shock. We aimed to analyze it and determine the relationship between Nesfatin-1 levels and quick Sequential Organ Failure Assessment(qSOFA) score, renal Sequential Organ Failure Assessment (SOFA) score, and mortality in patients with sepsis and septic shock. Sixty-nine hospitalized adult patients diagnosed with sepsis and septic shock in the internal medicine department, were included in the study after approval of the Clinical Research Ethics Committee. Sepsis diagnosis was based on the detected focus of infection, positive blood cultures, and response to antibiotics. Twenty-one healthy controls matched for age and sex with these patients were also included in the study. Sixty-nine septic patients and twenty-one healthy volunteers were included in the study. Nesfatin-1 levels were compared with covariates. Nesfatin-1 levels in septic patients were lower than that of healthy controls. There was no significant difference in Nesfatin-1 between diabetic and non-diabetic subgroups. Patients with quick Sequential Organ Failure Assessment (qSOFA) score of three had a statistically significantly lower Nesfatin-1 level than those of patients with the score of zero, one, and two. Nesfatin-1 was correlated negatively with C reactive protein. We found a statistically significant difference in 1-month mortality between Nesfatin-1 levels below and over 80pg/mL. In order to use Nesfatin-1 as a biomarker in differentiating sepsis from healthy population, more comprehensive and more studies are needed. If supported by new studies, Nesfatin-1 levels below 80 pg / mL at first admission in septic patients may direct the clinician to broad-spectrum antibiotic therapy and earlier intensive care follow-up.

Keywords: Nesfatin-1, sepsis, septic shock, biomarker

1. Introduction

Nesfatin-1, which was first detected in the hypothalamus of mice, is a recently discovered peptide with a half-life of 23.5 minutes derived from a precursor protein, nucleobindin 2 (NUCB2), (1, 2). In particular, its anorectic effect has been demonstrated in many studies. In this respect, intracerebroventricular injection has been shown to dose-dependently reduce food intake in newborn chicks and to have an anorectic effect (3) and to reduce food intake after central injection (4) in animals. It is important to note that it is co-localized with ghrelin in gastric X / A-like cells in mice and in P / D1 cells of humans, which creates the hypothesis that peptide products are stimulated by insulin in X / A-like cells: so, food intake is either stimulated by ghrelin or via nesfatin-1. is inhibited (5). Administration of Nesfatin-1 in renal ischemic mice has been found to cause a significant decrease in creatinine levels, indicating the future therapeutic effect of Nesfatin-1 (6). It has been shown to cross the blood-brain barrier and it has an opposite effect on food intake with Ghrelin (7). Recently, a large number of studies were published investigating the effects of Nesfatin-1.

On the other hand, sepsis is an inflammatory process in which appetite decreases. Studies in the current literature analyzed the course of Nesfatin-1 in chronic events such as malignancy and diabetes mellitus (8, 9). Still, the literature data is insufficient in acute conditions like sepsis. In order to correct this deficiency and in line with the knowledge that Nesfatin-1 protein is anorectic, we expect its level to decrease in sepsis and septic shock.

In accordance with the knowledge that Nesfatin-1 is an anorectic protein, we expect it to decrease during sepsis and septic shock and we aimed to analyze this condition. Another

* Correspondence: hasaneruzun@gmail.com

aim of our study was to determine the relationship of Nesfatin-1 levels and quick Sequential Organ Failure Assessment (qSOFA) score, C reactive protein (CRP), procalcitonin, lactate and creatinine levels, hourly urine output, renal Sequential Organ Failure Assessment (SOFA) score, leukocyte count, and mortality in patients with sepsis and septic shock.

2. Materials and methods

2.1. Patients and clinical data collection

Based on the results of the published generation, we aimed to determine the difference in 1 unit Nesfatin 1 with 80% power. A sample size of at least 17 diseases per group is required to predict the impact measurement of 1 (alfa: 0,05)

Sixty-nine hospitalized adult patients diagnosed with sepsis and septic shock in the internal medicine department, were included in the study after approval of the Clinical Research Ethics Committee (date: 21.01.2016 no: 48670771). Sepsis diagnosis was based on the detected focus of infection, positive blood cultures, and response to antibiotics. Twenty-one healthy controls matched for age and sex with these patients were also included in the study. Patients who were under 18 years of age, did not give consent to participate in the study, had malignancy, were obese (Body Mass Index >35), or were diagnosed with schizophrenia/anorexia nervosa were excluded from the study.

2.2. Measurement of serum Nesfatin-1 levels

The nesfatin-1 level was determined in all patients and control samples. Venous blood samples were centrifuged at 1000xg for 20 min. Blood was collected in Eppendorf tubes and plasma samples were saved at –80C. All stored blood samples were dissolved only once on the analysis day and serum Nesfatin-1 levels were measured by using Enzyme-Linked Immune Sorbent Assay (ELISA) kits. The linear measurement range was: 1.5ng/ml-300ng/ml. The reported intraassay and intraassay CV's were <10% and <12%. The minimum detectable dose of Nesfatin-1 is typically less than 234.2pg/mL.

2.3. Data analysis

Serum CRP, procalcitonin, lactate, leukocyte counts, creatinine levels, and hourly urine output were recorded. In terms of leukocyte counts, patients were divided into three groups as follows:<4000 leukopenia, 4000-12000 normal, and > 12000 leukocytosis.

Renal SOFA score of each patient was calculated and patients were divided into 5 groups according to their creatinine values and urine outputs: creatinine: <1.2 mg/dL (0 point), creatinine: 1.2-1.9 mg/dL (1 points), creatinine: 2-3.4 mg/dL (2 points), creatinine: 3.5-4.9 mg/dLorurine output 200-500 ml/day (3 points), creatinine: > 5 mg/dLorurine output <200 mL/day (4 points) (6-8). The outcomes of the patients hospitalized in the internal medicine service were evaluated (discharge, referral to the intensive care unit, death). The mortality rates of the patients were also analyzed.

2.4. Statistics

The Statistical Package for Social Sciences (SPSS) version 20 was used to analyze the data. It has been determined by the Kolmogorov-Smirnov test that gender, Nesfatin-1, lactate and creatinine levels and hourly urine output differ significantly from normal distribution. Therefore, non-parametric methods have been used in the analysis of these data. For non-normally distributed data we reported interquartile range. Significant differences were calculated using the Mann–Whitney U test and Kruskal Wallis test for continuous variables. Spearman's rank correlation was used to examine the relationship between two continuous variables. Age, CRP, procalcitonin values were normally distributed and parametric tests were used to analyze the data on these values (one-way ANOVA, independent samples t-test). Descriptive statistics (frequency, mean, standard deviation, and minimum, maximum, median) of the variables were calculated. P values of less than 0.05 were considered statistically significant.

3. Results

Sixty-nine septic patients and twenty-one healthy controls were included in our study. The demographic and clinical characteristics of our patients are presented in Table 1. There was no statistically significant difference between patients and healthy individuals regarding age or gender (Table 1).

Table 1. Characteristics of patients and healthy controls

	Septic patients (n:69)	Control group (n:21)	P
Gender (male/female)	39/30	8/13	0.139*
Age (year)	62.3 ± 17.6	50.8 ± 10.9	0.114*

*analyzed by independent Sample t test

As shown in Table 2, Nesfatin-1 levels were significantly lower in patients with sepsis and septic shock (median: 674.70 pg/ml, IQR: 169.60 – 1010.90pg/ml) compared to healthy controls (median: 902.10 pg/mL, IQR: 724.95 - 1370 pg/mL) (p=0.005). There was also statistically significant difference in CRP levels (p<0.001) (Table 2).

Table 2. Median Nesfatin-1 levels and mean CRP levels of patients and control group

	Sepsis (n:69)	Control (n:21)	P
Nesfatin-1 (pg/mL)	674.70 (169.60-1010.9)	902.10 (725-1370)	**0.005***
CRP (mg/L)	220.52±140.77	2.99±1.9	**<0.001****

*analyzed by Mann-Whitney-U test; ** analyzed by independent Sample t test

In our study, a negative correlation was found between Nesfatin-1 and CRP levels (p: 0.007, r: -0.250) (Fig. 1). When Nesfatin-1 levels were compared between the groups with and without diabetes mellitus, the difference was statistically non-significant. However, CRP values were statistically significantly different between diabetic sepsis (287.63 mg/L±162.98) and nondiabetic sepsis (189.9 mg/L ±118.35) patients (p: 0.038) (Table 3).

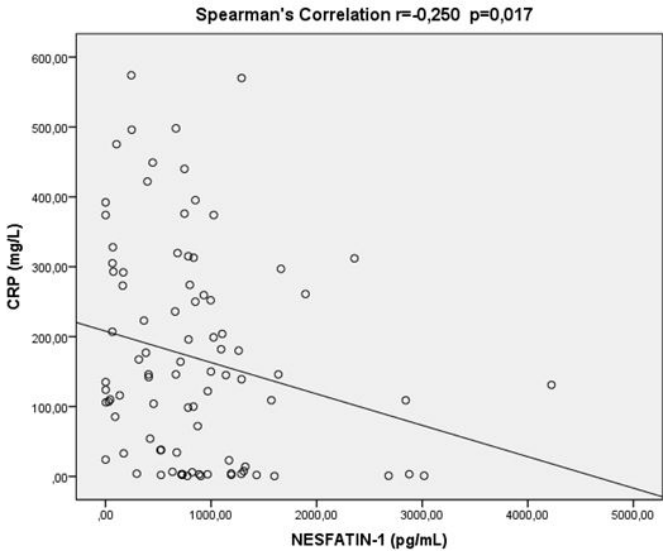

Fig. 1. The scotter plot of nesfatin and C-reactive protein

Table 3. Median Nesfatin-1 levels and mean CRP levels of patients with or without diabetes mellitus

	Sepsis with diabetes (n=22)	Sepsis without diabetes (n=47)	p
Nesfatin-1 (pg/mL)	764.80 (246.95 - 1045)	666.80 (90.90-998.80)	0.435*
CRP (mg/L)	287.63±162.98	189.1±118.35	**0.038****

*analyzed by Mann-Whitney-U test; ** analyzed by independent Sample t test. CRP: C-Reactive Protein

There were no significant differences in procalcitonin, creatinine or lactate levels, hourly urine output, qSOFA score, renal SOFA score, or leukocyte count (for all of them p > 0.05).

In contrast to CRP, there was no correlation between Nesfatin-1 levels and qSOFA score, procalcitonin, lactate, and creatinine levels or hourly urine output (p> 0.05 for all) (Table 4).

Table 4. Correlation between Nesfatin-1 levels and other parameters

	Nesfatin-1 (r)*	Nesfatin-1 (p)*
CRP	-0.250	0.017
Procalcitonin	0.128	0.294
qSOFA	-0.230	0.058
Lactate	-0.093	0.446
Creatinine	-0.42	0.733
Hourly Urine Output	0.016	0.896

*analyzed with Spearman's Correlation, CRP: C-Reactive Protein, qSOFA: quick Sequential Organ Failure Assessment

Nesfatin-1 levels did not differ significantly in different renal SOFA scores (p: 0.853). When the outcomes of 69 septic patients were assessed; 33 patients were discharged from the internal medicine department (19 patients over 65 years of age, 13 of whom were diabetic), 4 patients died (2 patients over 65 years of age, no diabetic patients), and 32 patients were referred to ICU (21 patients over 65 years of age, 9 were diabetic). Of the 32 patients referred to the ICU, seven were discharged (six were older than 65 years of age, three were diabetic) and 25 died (15 were older than 65 years of age; six were diabetic). Of the 42 septic patients over the age of 65 years, 19 died in the outcome assessment of their internal medicine hospitalization. Mortality rates of patients with sepsis were found to be independent of diabetes and age (over 65 years of age and below 65 years of age) (p: 0.722).

There was no statistically significant difference in terms of Nesfatin-1 levels in septic patients who were discharged, and patients referred to ICU during the hospitalization or compared with patients who died during the 1-month follow-up (p: 0,694; p: 0,821, respectively).

Also, when we evaluated 1-month mortality, we found that 35 of 69 patients died (50.72% mortality) and 34 of them were alive. Of 12 septic patients with Nesfatin-1 levels below 80 pg / mL, 10 (83.33% mortality) died while among nine patients with Nesfatin-1 levels above 1300 pg / mL, only 2 (22.22% mortality) died.

In our study, we can say that the mortality increased below 80 pg / mL Nesfatin-1 (arbitrary cut off) and the mortality decreased above the 1300 pg / mL Nesfatin-1 (arbitrary cut off) level. In other words, 10 (28.57%) of 35 patients who died during 1-month follow-up had a Nesfatin-1 value below 80. On this result, we divided the patients into two subgroups as patients with Nesfatin-1 values below 80 and over 80, and we found statistically significant differences in the 1-month mortality of patients (p: 0.013). Table 5 shows the distribution of Nesfatin-1 levels in 1-month mortality assessment on the survivors and non-survivors.

Table 5. Distribution of Nesfatin-1 in death and survivor patients in 1-month mortality assessment

Nesfatin-1 Levels (pg/mL)	Patients (n=69)	Control (n=21)
0-80 n (%) [Death(n)/ survivor (n)]	12 (17.4) (10/2)	0(0) (0/0)
80-500 n (%) [Death(n)/ survivor (n)]	17 (24.6) (8/9)	1 (4.7) (0/1)
500-1300 n (%) [Death(n)/ survivor (n)]	31 (44.9) (15-17)	11 (52.4) (0/11)
1300-4224 n (%) [Death(n)/ survivor (n)]	9 (13.1) (2-7)	9 (42.9) (0/9)

There was not any significant association between 1-month mortality and procalcitonin (p: 0.398), lactate (p: 0.606), and creatinine (p: 0.408) levels, hourly urine output (p: 0.104), renal SOFA score, qSOFA score, or leukocyte count (p: 0.714). However, there was a significant difference between the survivors and non-survivors in terms of CRP levels (p <0.05). The mean value of CRP was 186.5 mg / L in patients who died, and it was 255.4 mg / L in survivors.

4. Discussion

Sepsis is an inflammatory process in which appetite decreases. In sepsis, a clinical diagnosis, there is still no strong laboratory parameter to predict mortality today. A biomarker that predicts early mortality in septic patients will

be invaluable to clinicians.

Nesfatin-1 is a multifunctional, anorectic-acting peptide hormone with a half-life of 23.5 minutes (2). Studies conducted until this time investigated the course of Nesfatin-1 in chronic conditions such as malignancy, Polycystic Ovary Syndrome or Diabetes Mellitus. Nesfatin-1 level was reported to be significantly decreased in lung cancer (11). However, the data about the alterations in Nesfatin-1 levels in acute conditions is limited.

In our study, we compared the Nesfatin-1 levels in septic patients and healthy volunteers, and we found that Nesfatin-1 levels were significantly lower in septic patients. Our study was the first in the literature evaluating the Nesfatin-1 levels in sepsis and septic shock.

We further grouped septic patients as diabetic and nondiabetic and Nesfatin-1 levels did not differ between these two subgroups. However, in previous studies, serum Nesfatin-1 levels were found to be higher in patients with prediabetes and Type 2 Diabetes Mellitus (8,9). This information suggests that the Nesfatin-1 level is high in diabetic patients when there is no septic event, but it seems to be low in septic patients like non-diabetic patients. The fact that the Nesfatin-1 protein can be used as a marker in the diagnosis of sepsis; it is a promising result that Nesfatin-1 levels are not affected by the presence of diabetes. In addition, in this study, a negative correlation was found between Nesfatin-1 levels and CRP. These data suggest that Nesfatin-1 may be as reliable as CRP in the diagnosis of infection but may be superior to CRP due to the lack of affected results in diabetic patients because the CRP value was significantly different between diabetic and nondiabetic septic patients in our study. In rats with renal ischemia, the administration of Nesfatin-1 caused a significant decrease in creatinine levels and this was thought to indicate the future therapeutic effects of Nesfatin-1 (12). However, in a study in which Saldanha et al compared hemodialysis patients and healthy controls, Nesfatin-1 levels did not show a significant difference between the two groups (13). Similarly, in our study, there was no correlation between creatinine levels, hourly urine output or renal SOFA score, and Nesfatin-1 levels. Our study differs from the study performed with mice, since there was no relationship between kidney damage and Nesfatin-1 levels in our study performed with patients equally distributed according to renal SOFA score. In this respect, our study is the second human study showing that there is no relationship between Nesfatin-1 levels and kidney damage.

In addition, we did not find any correlation between Nesfatin-1 levels and procalcitonin, or lactate levels or leucocyte counts.

Nesfatin-1 values did not differ significantly in different qSOFA scores. However, when we combined the patients with qSOFA scores zero, one and two in a single group and three in a separate group, and compared these two groups, a statistically significant difference was observed in terms of Nesfatin-1 levels. Although more studies are warranted, this result suggests that Nesfatin-1 protein such as qSOFA, can be used for rapid evaluation of sepsis and may provide us an objective data in clinical practice.

There was not any significant difference between the patients who survived or died in the 1-month follow-up. However, the median Nesfatin-1 levels of the patients who died in the early period and who did not need to be followed up in the ICU at early periods (discharged from the service) were 54.03 pg / mL and 674.70 pg / mL, respectively. However, this difference did not reach a statistically significant level most probably due to the small number of septic patients who died at early periods (n: 4). If larger studies with more patients would be performed, it may be suggested that early ICU follow-up would be more appropriate in patients with lower Nesfatin-1 levels and a more aggressive treatment decision may be taken. Thus, this protein will be an important source of light for clinicians in the follow-up of patients, in the decision of treatment and in the unit to be followed.

When we evaluated 1-month mortality, 50.72% of the patients died. Previous studies have reported that in-hospital mortality rates due to sepsis are between 10 and 52% (14-17). In our study, the mortality rate in internal diseases wards was 5.7%, while in-hospital mortality rate was 42% that was in parallel with the current literature. Although most deaths are seen within the first six months, it is known that the risk continues for two years (18-22). In our study, 40 patients were discharged after hospitalization due to sepsis but six of them died within 1 month. This data supports the increase in mortality after hospitalization due to sepsis. One point we would like to draw attention to here is that the sensitivity and specificity of the cut off value for the Nesfatin-1 levels were too low for clinical use. However, 83.33% of patients with Nesfatin-1 levels below 80 pg / mL and 22.22% of patients with more than 1300 pg / mL died. Based on this information, we found that the mortality rate increased below the value of 80 pg / mL, which we determined as arbitrary cut off in our study, and we can still say that the mortality rate was lower in patients with Nesfatin-1levels higher than 1300 pg / mL, which was again determined as an arbitrary cut-off.

In the same way, the lowest Nesfatin-1 level in our control group was 296 pg / mL. Although larger studies with a higher number of patients and the control cases are required, we would like to note that we had Nesfatin-1 levels lower than 296 pg / mL only in the septic patient group. This value can serve as a valuable parameter in evaluating patients as sepsis and it may be associated with poor prognosis. However, it is obvious that more studies are warranted.

Furthermore, supporting our findings, as indicated in the kit procedure it was noted that the value of the Nesfatin-1

protein at a concentration close to zero was indicated to be at a sensitivity of 234.2 pg / mL. In parallel with this information, there was no value less than 234.2 pg / mL in the control group, but it was below the value specified in three of four patients who were expired during their hospitalization. This suggests that Nesfatin-1 protein is too low to be detected in early-onset sepsis.

We did not find any association between 1-month mortality and procalcitonin, lactate or creatinine levels, hourly urine output, renal SOFA score, qSOFA score, or leukocyte count. However, there was a significant difference in terms of CRP levels among survivors and expired patients within 1 month. The mean value of CRP was 186.5 mg / L in the expired group, and it was 255.4 mg / L in survivors. However, since both values were clinically high, we think that this result has no clinical significance.

In previous studies, it has been emphasized that low procalcitonin levels in septic patients would negatively affect prognosis since it may cause misdiagnosis (23-28). In our study, we did not find a correlation between procalcitonin levels and in-hospital or 1-month mortality. Therefore, we believe that procalcitonin should not be used in the clinical prognostic approach.

In our study, we did not find a relationship between qSOFA score and in-hospital or 1-month mortality. However, mortality is estimated to be more than 10% in patients who meet all of the qSOFA criteria in the literature (29). The fact that the qSOFA score, which has been in use since 2016, has not predicted mortality in our study shows that more studies are required in this regard.

In past publications, the anti-inflammatory and antiapoptotic properties of Nesfatin 1 have been emphasized (30). It is known to inhibit neutrophil infiltration. Due to this effect, it is an expected finding that the level of Nesfatin 1 decreases, as the anti-inflammatory effect may need to be suppressed in a situation where inflammation is intense such as sepsis and septic shock. In our study, a result in this direction was obtained.

Our study has some limited aspects. The first is the limited number of patients. The sensitivity and specificity of some markers may not have reached statistical significance. The area we want to mention in this regard is the comparison with the patients who were mortal in the early period. The second restricted aspect of our study was that all samples were not taken before the first antibiotic dose, which weakened the results and may showed higher Nesfatin-1 values in the septic group. Thirdly, since we did not report the infection focus and type of infection (microbial agent) of septic patients, we were unable to group accordingly and could not evaluate its effects on prognosis. Fourthly, we did not evaluate the level of NUCB2 protein or NUCB2 gene expression. Fifthly, Sepsis has many prognostic factors including early recognition and management of sepsis, appropriate antibiotic treatment initiation time, antibiotic resistance profile of infectious agent, APACHE scores, co-morbidities and age, etc. Therefore, evaluation of prognostic value of any test requires analysis of the test value together with confounder factors. We could not analyze the confounder factors. Finally, we did not state the causes of death.

Nesfatin-1 level was lower in septic patients compared to healthy controls and had a negative correlation with CRP. This does not differ in diabetic and nondiabetic septic patients in contrast to CRP. Nesfatin-1 can be used as a biomarker for differentiation of healthy population with sepsis. In patients with qSOFA score 3, the fact that Nesfatin-1 protein was lower than those with qSOFA score of 0, 1 and 2 indicates that this protein can be used in the rapid evaluation of sepsis and it may give us clinical benefit as an objective data.

Furthermore, Nesfatin-1 levels below 80 pg / mL in septic patients at the time of admission to the hospital may lead the clinician to early ICU follow-up with antibiotic therapy, with a broader spectrum and less resistance.

It is evident that prospective randomized controlled trials with a greater number of cases are warranted for the use of serum Nesfatin-1 levels in the diagnosis of sepsis and the prediction of mortality.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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