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Original Research

Investigation of the Effectiveness of Nutrition at the Molecular Level in Patients with Sepsis

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ABSTRACT

Objective: The aim of this study was to compare inflammatory and anti-inflammatory molecule levels in sepsis patients receiving normal (1.3 mg/kg/day) and high (2 mg/kg/day) protein supplementation.

Methods: Two groups of patients were compared based on protein supplementation: normal (1.3 mg/kg/day) and high (2 mg/kg/day). Levels of kallistatin, nesfatin-1, plasminogen activator inhibitor-1 (PAI-1), and high mobility group box-1 (HMGB-1) were measured. Disease severity was assessed using APACHE II, SAPS, and SOFA scores.

Results: Demographic characteristics and intensive care scores were similar between groups ($p>0.05$). Group 1 had significantly higher 0-hour levels of HMGB-1, kallistatin, PAI-1, and nesfatin-1 compared to 24 and 48 hours ($p<0.001$). Group 2 had higher 0-hour levels, but changes were not significant ($p>0.05$)

Conclusions: High-dose protein feeding in sepsis patients may not suppress inflammation-related protein synthesis despite the presence of oxidative damage and muscle catabolism.

Keywords: Sepsis, Biomarker, Kallistatin, Plasminogen Activator Inhibitor-1, Nesfatin-1, High Mobility Group Box-1, protein diet

INTRODUCTION

Sepsis is a syndrome accompanied by physiological, pathological and biochemical abnormalities induced by infection and is a serious public health problem. Although its true incidence is unknown, it is estimated to be one of the leading causes of mortality worldwide [1].

Septic shock is a condition characterized by a mortality risk much higher than sepsis alone, accompanied by circulatory system disorders, cellular and metabolic abnormalities, the need for vasopressors to maintain mean arterial pressure at or above 65 mmHg, and a serum lactate level above 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. In the presence of these two findings, the mortality risk is higher than 40% [1].

Sepsis and related status septic shock have high mortality rates ranging from 20% to 50% even today. Although it is necessary to determine the causative microorganism, culture tests are not always useful due to their time-consuming and low sensitivity [2].

The SOFA and APACHE 2 scores are frequently used to assess the severity of sepsis. The use of these scoring systems is quite complex and time-consuming. It may not always be possible to collect the parameters required for scoring. Therefore, a biomarker that can be easily measured is needed to more easily assess the severity of sepsis [2].

Malnutrition, especially sepsis, is associated with increased morbidity and mortality in intensive care patients, and nutritional support is extremely important in the standard care of these patients. Sepsis is characterized by proinflammatory metabolic response, increased energy consumption, accelerated catabolism, and hyperdynamic circulatory changes. In this context, a decrease in lean body mass, organ function, and immune function deterioration occur in sepsis patients, and if this condition persists for a long time, conditions such as protein energy malnutrition, increased infectious morbidity, artificial respiration dependency, increased intensive care and hospital stay, and increased mortality may occur.

The aim of this study was to compare the levels of inflammatory and anti-inflammatory molecules in patients with sepsis who were fed 1.3 mg/kg/day protein supplementation and 2 mg/kg/day protein supplementation.

MATERIAL AND METHODS

The study was initiated by the Gaziantep University Faculty of Medicine Clinical Research Board with the decision number 178 dated 08.05.2019. This study was supported by Gaziantep University Scientific Research Projects with the project number TF.UT.19.20. The study was conducted prospectively with sepsis patients admitted to the Gaziantep University Faculty of Medicine, Department of Internal Medicine, Intensive Care Unit (ICU) between 10.05.2019 and 01.08.2019. Our study adhered to the principles outlined in the Helsinki Declaration. Written consent was obtained from the patient and relatives.

Main Points

- In our study, the results of nutritional status in sepsis patients, which cause decreased muscle strength, prolonged ventilator dependency, increased healthcare costs and high mortality due to increased protein catabolism, were examined. Although many heterogeneous data in the literature claim that high protein diet can prevent muscle breakdown, our study showed that high protein diet cannot suppress the increase in various inflammatory markers.

Aim of Work

This study investigated whether normal and high dose protein nutrition had a positive effect on inflammation markers and levels in patients with sepsis.

Case Selection

This study was prospectively examined with sepsis patients admitted to the intensive care unit. Volunteer patients who were diagnosed with sepsis according to the definitions determined by the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) Sepsis 3 meeting, whose intensive care stay lasted longer than 24 hours, who were over the age of 18, and whose informed consent form was signed by the patient or their relatives were included in the study. Patients with any known inflammatory disease or active malignancy were excluded from the study.

According to nutritional status, patients were divided into two groups as group 1 (1.3 grams/kg/day) and group 2 (2 grams/kg/day) protein recipients according to the recommendations of the American Society for Parenteral and Enteral Nutrition (ASPEN). All selected patients were fed enterally via nasogastric tube. Patients who could be fed orally and received parenteral nutrition support were not included in the study. Patients who could not tolerate feeding via nasogastric tube or could not tolerate receiving targeted protein support during the study and who developed shock were excluded from the study. Fresubin® Original Fibre (Fresenius Kabi İlaç San. ve Tic. Ltd. Şti) was given as the nutritional content for the patients in order to provide the targeted protein content.

APACHE II, SAPS and SOFA score values from intensive care scoring systems showing disease severity in the patient group were used. APACHE II, SAPS and SOFA scores of the patients included in the study were calculated using the parameters analyzed in the first 24 hours after admission to the intensive care unit.

Demographic data of the patients, accompanying disease status, APACHE II, SAPS and SOFA scores calculated for the first 24 hours of hospitalization, leukocyte count, C-reactive protein and procalcitonin values measured on the day of hospitalization were recorded.

Lab Investigations

Blood samples sent to the laboratory for routine test analysis were kept for 30 minutes and then centrifuged at 3500 rpm for 15 minutes. After centrifugation, patient sera were placed in Eppendorf tubes and stored at -80C until the study day for the analysis of tests called nesfatin-1, kallistatin, plasminogen activator inhibitor protein-1, and high mobility group box-1. High mobility group box-1 (HMGB1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels were determined by sandwich-ELISA method.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences software version 24.00 (SPSS Inc., USA) program. Descriptive values were expressed as number (percentage) (n) (%) and mean ± standard deviation. According to the normality assessment of continuous variables made with the Kolmogrov-Smirnov and Shapiro-Wilk tests, the nonparametric test Mann-Whitney U test was used for those not conforming to normal distribution; and the Student t test was used for continuous data conforming to normal distribution. The Friedman test was used to compare continuous variables not conforming to normal distribution in dependent groups. The statistical significance level for all tests performed was accepted as $p<0.05$.

RESULTS

Demographic characteristics of the groups, intensive care scoring systems and statistical significance levels are shown in Table 1. No statistically significant difference was determined between the patient and control groups in terms of demographic characteristics ($p>0.05$).

Serum high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels and significance levels of group 1 patients are shown in Table 2. High mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin levels of Group 1 patients measured at hour 0 were determined to be high compared to the levels at hour 24 and hour 48.

Serum leukocyte count, neutrophil count, C-reactive protein and procalcitonin levels and significance levels of Group 1 are shown in Table 3. The zeroth hour leukocyte count, neutrophil count, C-reactive protein and procalcitonin levels of Group 1 patients were determined to be higher compared to the 24th and 48th hour levels.

Serum high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels and significance levels of Group 2 are shown in Table 4. Zeroth hour high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels of Group 2 patients were determined to be high compared to the 24th and 48th hour levels.

Serum leukocyte count, neutrophil count, C-reactive protein and procalcitonin levels and significance levels of Group 2 are shown in Table 5. The zeroth hour leukocyte count, neutrophil count, C-reactive protein and procalcitonin levels of Group 2 patients were determined to be higher compared to the 24th and 48th hour levels.

The comparison of the percentage changes in high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 between the groups at 0, 24 and 48 hours is given in Table 6.

Table 1. Comparison of demographic characteristics of groups

	Group 1 (30)	Group 2 (30)	p
Age*	65,73±13,76	61,40±15,45	0.256
Sex			0.300
Male,n(%)	20(%66,7)	16(%53,3)	
Female, n(%)	10(%33,3)	14(%46,7)	
Body weight kg)	77.5(71/95)	76(71/95)	0.608
Lenght (meter)	1.76(1.63/1.81)	1.76(1.63/1.81)	0.283
BMI (kg/m2)	25(22/34)	25(22/34)	0.316
APACHE II	18(11/43)	22(8/39)	0.343
SAPS	59(4/109)	59(28/80)	0.286
SOFA	10(3/17)	13(2/17)	0.190

APACHE II: APACHE II score, SAPS: SAPS score,

* Mean±standard deviation

Table 2. High mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin-1 levels of group 1 patients at 0, 24 and 48 hours

	Zeroth hour	24.th hour	48.th hour	p
HMGB-1	1.71(0.45/12.43)	1.04(0.07/13.58)	0.53(0.16/12.02)	0.001
Kallistatin	22.83(14.28/562.85)	16.88(2.57/522.39)	14.66(8.51/51.39)	<0.001
PAI-1	8.96(4.73/166.09)	7.66(0.63/195.14)	8(2/172)	0.967
Nesfatin-1	5.02(3.26/82.29)	3.67(0.41/81.06)	3.87(0.95/83.26)	<0.001

Table 3. Prealbumin, white blood cell count (WBC), neutrophil count, C-reactive protein (CRP) and procalcitonin (PCT) levels of Group 1 patients at 0, 24 and 48 hours

	Zeroth hour	24th hour	48.th hour	p
Prealbumin	11.20(4.10/30)	10.80(2.90/30.50)	10.70(3.30/28)	0.318
WBC	12660(6130/20640)	12470(5260/22160)	12880(5230/31790)	0.587
Neutrofil	10180(4100/18220)	10090(2640/19760)	11040(1860/24230)	0.670
CRP	90.02(10.4/206.50)	79.62(17.91/185.50)	65.80(15.16/227.80)	0.670
PCT	2.36(0.29/102.40)	1.85(0.22/51.98)	2.80(0.27/125.61)	0.008

Table 4. Nesfatin-1, kallistatin, plasminogen activator inhibitor-1 and high mobility group box-1 levels of group 2 patients at 0, 24 and 48 hours

	Zeroth hour	24.th hour	48.th hour	p
HMGB-1	0.60(0.14/0.93)	0.54(0.18/2.25)	0.67(0.16/1.13)	0.644
Kallistatin	15.23(11.08/45.34)	19.13(9.79/41.32)	16.59(6.88/26.01)	0.046
PAI-1	7.91(1.88/9.46)	7.01(1.44/10.11)	7.12(1.93/10.11)	0.670
Nesfatin-1	4.32(0.89/6.31)	4.83(0.86/6.37)	4.47(1.16/6.35)	0.079

Table 5. Leukocyte count (WBC), neutrophil count, C-reactive protein (CRP) and procalcitonin (PCT) levels of Group 2 patients at 0, 24 and 48 hours

	Zeroth hour	24.th hour	48.th hour	p
WBC	19860(1890/26650)	19420(4370/38950)	19020(1220/37890)	0.007
Neutrophil	16260(5500/21970)	14840(3850/34660)	15510(3690/33930)	0.061
CRP	191(44.20/297.30)	175.90(35.40/348.70)	159.80(5.47/450)	0.061
PCT	5.30(1.11/81.58)	4.50(1.10/39.48)	3.13(0.81/76.86)	<0.001

Table 6. Comparison of the percentage changes in high mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin among the groups at 0, 24 and 48 hours

	Group 1	Group 2	p
HMGB-1 24th hour change (%)	26.56	23.13	0.882
HMGB-1 48.hour change (%)	-55.45	7.60	<0.001
Kallistatin 24.hour change(%)	19.20	27.40	0.001
Kallistatin 48.hour change(%)	-24.33	-2.13	0.008
PAI-1 24.hour change(%)	-7.6	4.40	0.836
PAI-1 48.hour change(%)	-17.13	0.93	0.287
Nesfatin-1 24.hour change(%)	-27.4	6.23	<0.001
Nesfatin-1 48.hour change(%)	-37.77	6.07	<0.001

DISCUSSION

Sepsis is a clinical syndrome of physiological, biological, and biochemical abnormalities caused by a dysregulated inflammatory response to infection. Sepsis and the resulting inflammatory response can lead to multiple organ dysfunction and death. In the late 1970s, it was estimated that there were 164,000 cases of sepsis per year in the United States (US) [3]. Since then, sepsis rates in the US and elsewhere have been increasing steadily, although many are derived from academic institutions or from demand-based analyses [4,5]. Possible reasons for the increased incidence of sepsis include advancing age, immunosuppression, and the emergence of multidrug-resistant microorganisms [6,7]. Although this is not a proven hypothesis, increased awareness through education and awareness campaigns may be effective in early diagnosis of sepsis.

Sepsis is a life-threatening condition associated with a systemic inflammatory response to microbial infection [8]. Sepsis is the most common cause of death in intensive care units, with a fatality rate of 80% due to the development of multiple organ failure. Exaggerated systemic inflammatory mediator synthesis is thought to cause septic shock and death [9].

Despite many therapeutic interventions aimed at controlling the immune system in order to stop the progression to organ failure, the desired success may not be achieved [10]. This simple fact has led to an increase in studies on the pathogenesis of sepsis. In the United States, it causes 150,000 deaths per year, more than the combined deaths of patients with breast, colon, prostate, and brain tumors [11,12].

The onset and progression of systemic inflammation leads to the onset of sepsis and the onset of a hypermetabolic state at the cellular level [13]. Indicators of the septic immune response, such as high fever, increased protein synthesis, tachycardia, and tachypnea, require energy supply above physiological needs. Some sources state that daily energy needs in septic patients can be as high as 10,000 calories [14]. This hypermetabolic state cannot be compensated by high caloric support alone.

The decrease in total body mass during critical illness is a serious intensive care problem seen worldwide. Skeletal muscle proteins are the primary sources for the synthesis of immunoglobulins and acute phase reactants. Muscle protein loss occurs rapidly in critical care patients, and muscle loss associated with a deficiency in total body nitrogen balance of up to 18% can be seen, especially in the first 10 days of intensive care hospitalization. The extent of protein loss may be associated with morbidity and mortality [15,16].

Dietary amino acids must be added to the structure of functional proteins to protect them from oxidation due to their structure. Proteins in the structure of skeletal muscles are the largest protein depot in the body and respond to anabolic nutrition. Amino acids of muscle proteins can be rapidly released and used in stress situations such as starvation and sepsis. If a person does not have enough protein intake to meet daily protein requirements, a negative protein balance develops in the body and skeletal muscle atrophy, impaired muscle growth and a decrease in functional capacity occur. Especially in elderly patients, the decrease in food intake over time increases the risk of complications in geriatric intensive care patients.

Muscle growth depends on protein consumption and hyperaminoacidemia, which stimulates muscle synthesis and, to a lesser extent, reduces muscle protein. When dietary protein consumption is insufficient to meet daily requirements, skeletal muscle atrophy occurs due to negative protein balance. This results in impaired muscle growth and functional decline. It has been reported that the use of dietary amino acids for muscle protein synthesis is more blunted and impaired in healthy older adults compared to young people. Metabolic studies have shown that this anabolic resistance can be overcome with higher levels of protein/amino acid intake [17,18]. Many studies indicate that 25-30 grams/day protein intake is the optimum dose to stimulate maximum quality protein synthesis in adults [19-23]. It is thought that adequate protein supplementation should be the basic approach to preventing protein energy malnutrition and improves clinical outcomes [24,25].

In a study by Singer et al. published in the journal of the European Society of Clinical Nutrition and Metabolism (ESPEN), a daily protein intake of 1.3 grams/kg of protein is recommended during critical illness [26]. However, the same study also states that patients on a high protein diet have positive clinical outcomes. In a study by Weijs et al. including 886 patients, a reduction in 28-day mortality was reported in patients receiving 1.2-1.5 g/kg/day of protein [27]. In a study by Allingstrup et al., a dose-dependent improvement in survival was found in a study by high protein intake [28]. In a retrospective study, Song et al. showed that critically ill patients on mechanical ventilation who achieved 90% of the targeted protein intake had significant improvements in intensive care outcomes [29]. Various studies have suggested that daily protein intake in critically ill patients should be 2.0-2.5 grams/kg/day [30,31]. In this study, patients who were clinically diagnosed with sepsis according to Sepsis 3 criteria, could not be fed orally, and did not receive parenteral nutrition were included in the intensive care unit. The nutritional status of sepsis patients was arranged according to their body weight. They were divided into two groups according to their nutritional status as group 1 (1.3 grams/kg/day) and group 2 (2 grams/kg/day) protein recipients. All selected patients were fed enterally via nasogastric tube. Fresubin® Original Fibre was given as the nutritional content of the patients in order to provide the targeted protein content. The aim of this study was to determine the effects of normal and high-dose protein supplementation on inflammatory and anti-inflammatory proteins in critically ill patients with sepsis. For this purpose, High mobility group box-1 (HMGB-1), kallistatin, plasminogen activator inhibitor-1 (PAI-1) and nesfatin levels were examined.

High mobility group box-1 is a protein found in the nucleus and cytoplasm of almost all cell types. It is actively secreted by immune system cells in response to infection or injury. HMGB-1 is also a potent proinflammatory cytokine and is associated with inflammatory diseases such as sepsis. In our study, serum HMGB-1 levels increased by 26.56% at 24 hours compared to 0 hours in group 1 patients and by 23.13% in group 2 patients ($p=0.882$). However, while there was a 55.45% decrease in serum HMGB-1 levels at 48 hours compared to 0 hours in group 1 patients, a 7.60% increase was detected at 48 hours in group 2 patients. This situation shows that the HMGB-1 molecule, which has a half-life of 17 minutes, is synthesized more in patients fed with high doses of protein than in patients fed with standard doses of protein [32]. Therefore, high-dose protein supplementation in critically ill patients in order to prevent the destruction of muscle proteins may increase the synthesis of inflammatory proteins and increase the risk of inflammation, septic shock and multiple organ failure.

Kallistatin is an endogenous serine protease inhibitor and its serum level decreases in case of inflammation. In the study conducted by Lin WC et al. on 86 intensive care patients, it was determined that the serum kallistatin level was lower in patients with septic shock compared to patients with severe sepsis [33]. In our study, the serum kallistatin level increased by 19.20% at 24 hours compared to 0 hours in group 1 patients and by 27.40% in group 2 patients ($p<0.001$). However, while there was a 24.33% decrease at 48 hours compared to 0 hours in group 1 patients, a 2.13% decrease was detected at 48 hours ($p=0.008$). Although it is an anti-inflammatory molecule, the increase in serum levels in patients fed with high protein may be attributed to exaggerated nonspecific protein synthesis in the first 24 hours when the inflammatory cascade is triggered in sepsis patients with systemic inflammatory response syndrome at the center of their pathogenesis. This also reveals the fact that adequate protein support is necessary for the increase in the synthesis of anti-inflammatory molecules.

Plasminogen activator inhibitor-1 (PAI-1), an important regulator of fibrinolysis, has been identified as a potential biomarker for the diagnosis of sepsis. Plasminogen activator inhibitor-1 (PAI-1) inhibits plasminogen activator, a key enzyme involved in the cleavage of plasminogen into plasma. In a study of 363 patients by Tiope et al., it was found that PAI-1 levels were higher in

patients with severe sepsis compared to patients with sepsis [34]. In our study, serum plasminogen activator inhibitor-1 levels decreased by 7.60% at 24 hours compared to 0 hours in group 1 patients, while they increased by 4.40% in group 2 patients. However, in group 1 patients, there was a 17.13% decrease at 48 hours compared to 0 hours, while there was a 0.93% increase at 48 hours. The increase in PAI-1 levels, which is a part of the inflammatory process in sepsis patients fed with high doses of protein, has been interpreted as high protein replacement may trigger the inflammatory process.

Nesfatin-1 is a peptide secreted by peripheral tissues, central and peripheral nervous system. Nesfatin-1, which is related to food intake and water consumption, is related to energy homeostasis. Nesfatin-1 can cross the blood-brain barrier bidirectionally. In a study conducted by Özsavcı et al. on rats, it was revealed that the nesfatin-1 molecule has an anti-inflammatory effect [35]. However, in another study conducted with patients with chronic obstructive pulmonary disease, it was claimed that the nesfatin-1 molecule may have inflammatory effects [35]. In our study, serum nesfatin-1 level decreased by 27.40% in group 1 patients at 24 hours compared to hour 0 and increased by 6.23% in group 2 patients. However, while there was a 37.77% decrease in group 1 patients at hour 48 compared to hour 0, an increase of 6.07% was detected in group 2 patients at hour 48. The nesfatin-1 molecule may have different effects on inflammatory mechanisms in the central nervous system and the peripheral nervous system. The increase in serum nesfatin-1 levels in sepsis patients fed with high doses of protein has been interpreted as high protein replacement may trigger the inflammatory process.

CONCLUSION

Preservation of muscle mass and prevention of muscle protein breakdown in critical care patients is an important goal in reducing the duration of intensive care, the need for mechanical ventilation support, and the risk of complications. This need should be managed more carefully in diseases where the catabolic process is more intense, such as sepsis. Protein supplementation at a dose of at least 1.3 g/kg/day is recommended for critical care patients in order to prevent muscle breakdown. In our study, it was determined that the synthesis of many inflammatory molecules increased at 48 hours in the patient group receiving high-dose (2 g/kg/day) protein supplementation. There are not yet sufficient studies in the literature investigating the effect of high protein supplementation on the inflammatory process in critically ill patients. Prospective and randomized controlled studies with a larger number of patients are needed to support our study data.

Conflict of interest: None declared.

Informed Consent: Received.
Informed Consent: Written permission was obtained from the patients

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Ethical Approval: The Gaziantep University Clinical Researches Ethics Committee authorized the research design (Approval date: 08.05.2019).

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