Serum Amino Acid Levels and Mortality in Patients Undergoing Percutaneous Endoscopic Gastrostomy

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ABSTRACT

Objective: To evaluate the effect of feeding *via* percutaneous endoscopic gastrostomy tube (PEG) on serum amino acid levels and mortality.

Study Design: Descriptive study.

Place and Duration of Study: University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey, from January 2016 to February 2019.

Methodology: Patients over 18 years of age, who were indicated for PEG due to loss of swallowing reflex, were included in the study. The follow-up period of the study was one year. The patients were reevaluated on the 3rd, 6th, and 12th months after inclusion. Anthropometric measurements, and nutritional status were evaluated at each visit, and quantitative amino acid levels were analysed. Statistical significance was accepted as $p < 0.05$.

Results: The study was carried out with a total of 53 cases (23 men and 30 women) ranging in the age from 18 to 91 years. While 13 patients were still alive, 40 patients died before completing one year. The levels of glutamine, leucine, taurine, and threonine were significantly different between surviving patients and dead. A statistically significant difference was found between the levels of citrulline ($p < 0.001$), ornithine ($p = 0.036$) and tyrosine ($p = 0.011$) during the four different visits of patients who survived. In patients who died, a significant difference was found between the levels of threonine, ornithine, and aspartic acid ($p < 0.043$ for all) between visits. Citrulline and tyrosine levels were found to be significantly increased in surviving patients.

Conclusion: The amino acid profiles of malnourished patients vary considerably. Increase in citrulline, ornithine and tyrosine levels are noted in surviving patients.

Key Words: *Amino acid, Percutaneous endoscopic gastrostomy, Malnutrition, Mortality.*

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INTRODUCTION

Malnutrition is a syndrome that can lead to negative consequences such as progressive and widespread loss of muscle mass and strength, physical dependence, falls, low quality of life, and death; and can be seen in children and the elderly.[1] Metabolic disorders of patients with malnutrition are quite complex.[2] Malnutrition is an important catabolic process leading to a peripheral energy deficit caused by fragmentation of muscle proteins and increased oxidation of branched chain amino acids.[3] Studies have shown correlations between the clinical status and specific laboratory values of malnourished patients.[4]

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However, there is no study showing the relationship between amino acid values and mortality rate in patients who were feeding with percutaneous endoscopic gastrostomy (PEG). The prognosis in any case of malnutrition is difficult to predict, but theoretically should be related to the degree of disruption in peripheral energy deficit. PEG is an indicated method for patients with normal gastrointestinal function, who require long-term enteral feeding.[5] PEG is a palliative option for the prevention of malnutrition in cases with decreased / loss of swallowing reflex, except for terminal stage patients whose life span is less than 1-2 months.[6] This study was conducted to evaluate the effect of feeding with PEG tube on mortality and quantitative serum amino acid levels.

METHODOLOGY

This study was designed as a prospective and self-controlled study. Ethics committee approval was obtained. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and

national research committee and with the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards. For the power analysis, the study by Su *et al.* was used as reference.[7] Considering the correlation coefficient between sequential organ failure assessment score and taurine (r=-0.319), the sample size was calculated as minimum 55, with a type 1 error of 0.05, and the strength of the study being 80%. With a 20% loss, a total of 53 patients were incorporated in the study. Fifty-three patients over the age of 18 with PEG indication, who were hospitalised following the loss of swallowing reflex due to aging (age-related decrease in swallowing reflex) or neurological disease (chronic cerebrovascular disease, dementia, alzheimer's disease), were included in the study. Patients were included in the study in order of hospitalisation.
Patients under the age of 18, who were feeding parenterally in the first 48 hours of hospitalisation, and with a history of major surgery, were not included. A detailed history was taken, and physical examinations were performed. The patients were reevaluated on the 3rd, 6th, and 12th months after first assessment.

The heights of the patients were measured with a height meter. Since most of the patients were bed-ridden, the last known weight of the patient was the current weight of the patients since the beds in the hospital do not have weight measurement features. Body mass index (BMI; Kg / m^2) was calculated using these measurements. Upper arm and calf circumference measurements were performed using a tape measure. Measurements of arm circumference below 22 cm as low, and 22 cm and above as normal for men and below 20 cm as low, 20 cm and above as normal for women. Calf circumference below 31 cm: low, 31 cm and above: normal for men; and below 28 cm: low, 28 cm and above: normal for women.[8]

The mini nutritional assessment (MNA) questionnaire was used to evaluate the nutritional status of the patients. Assessment was as follows: under 17 points: malnutrition, between 17 and 23.5 points: under the risk of malnutrition, between 24 and 30 points: normal nutritional.[9]

Blood samples were taken from 8:00 am to 10:00 and analysed simultaneously. Blood glucose levels were analysed in whole blood by the enzymatic calorimetric methods, using commercial devices. Calcium, phosphorus, alanine transaminase, aspartate transaminase and albumin levels were measured using the enzymatic colorimetric test with a Hitachi 747 auto analyser (Mito, Ibaragi, Japan). Creatinine level with Jaffe`, C-reactive protein with immunoassay, blood urea nitrogen level with spectrophotometer, potassium, and sodium with ion selective electrode were measured (Architect plus device, Abbot Diagnostics, Abbot Park, IL). Quantitative amino acid levels were measured using the tandem mass spectrometry technique, while GC-mass spectrometry was measured using the HPLC method (ARCHITECT i2000SR immunoassay analyser, Abbot Diagnostics, Abbot Park, IL).

Patients included in the study were divided into four groups as 0th month, 3rd month, 6th month, and 12th month.

Power analysis was performed for sample size. The Statistical Package for the Social Sciences (SPSS) software programme, version 22.0 (IBM) was used. Descriptive statistical methods [mean ± standard deviation, median (IQR: 25th percentile-75th percentile), frequency and percentage] were used to evaluate the study data. The paired sample t test was used for intragroup comparisons of quantitative data showing normal distribution, while the Wilcoxon signed ranks test was used for intragroup comparisons of parameters with abnormal distribution. The Friedman test was used to test whether the mean rank differed significantly from each other in the related measurements. ROC analysis was used to evaluate the relationship between survival times. The Cox regression (or proportional hazards regression) is a method for investigating the effect of several variables on the time a specified event (mortality) takes to happen. In the context of an outcome such as death, this is known as Cox regression for survival analysis. Significance was accepted as $p < 0.05$.

RESULTS

The study had a total of 53 cases, 23 of whom were men (43.4%) and 30 women (56.6%), ranging in age from 18 to 91 years. The mean age was 78.53 ± 13.39 years. In survival analysis, 40 of 53 patients included in the study died. The last death was seen on the 318th day, and the cumulative survival rate on this date was 25%.

At the end of the present study, 40 (75.5%) patients died while 13 (24.5%) patients were alive. In the ROC analysis made by dividing the patients into two groups as patients who survived and patients who died, the cut-off values and the values under the curve of amino acids such as 3rd month glutamine (AUC=0.762, 95% C.I: 0.565-0.958), 3rd month leucine (AUC=0.715, 95% C.I: 0.501-0.930), 6th month leucine (AUC=0,762, 95% C.I: 0.541-0.982), 6th month taurine (AUC=0,723, 95% C.I: 0.502-0.944), and 6th month threonine (AUC=0,754, 95% C.I: 0.528-0.980) were found to be statistically significant ($p < 0.05$; for all, Figure 1).

A statistically significant difference was found between the measurements of citrulline, ornithine, tyrosine at 0, 3, 6, and 12 months in during four visits of 13 patients who survived ($p < 0.001$; p: 0.036; and p: 0.011, respectively, Table I). There was no difference in other amino acid levels between visits.

In the analysis of patients who died, the 6th month threonine values increased significantly compared to the baseline threonine values. Aspartic acid values increased at the 6th month compared to the 3rd month. There was also a significant increase in the 6th month ornithine values compared to the baseline ornithine values (Table I). Parameters found to be significant, which are MNA 0th month, bed sores 6th month, upper arm circumference (cm) 0th month and transferrin 0th month in the comparisons made according to survival, were included in the multivariate Cox regression analysis. The Cox regression model was found as significant, and could be interpreted ($p = 0.013$). The 6th month bed sore was found to be significant ($p=0.046$). A one unit change in 6th month bed sore increases the death status by 4.512 (95% CI for HR: 1.026-19.835).

Table I: Comparison of amino acids with significant changes between visits.

	Patients who survived (n=13)	p*		Patients who died (n:40)	p**
	Median (IQR: 25th percentile-75th percentile)			Median (IQR: 25th percentile-75th percentile)	
Citrulline 0th Month	17.8 (11.8-21.0) µmol/L	<0.001	Threonine 0th month	98.1 (80.4-129.4) (µmol/L)	0.043
Citrulline 3rd Months	26.4 (20.8-45.1) µmol/L		Threonine 3rd month	123.75 (98.0-144.5) (µmol/L)	
Citrulline 6th Months	31.9 (29.5-46.8) µmol/L		Threonine 6th month	126.0 (124.0-144.0) (µmol/L)	
Citrulline 12th Months	43.21 (32.2-58.4) µmol/L	-	Threonine 12th month	-	-
Tyrosine 0th Month	37.8 (35.5-46.1) µmol/L	0.036	Ornithine 0th month	81.9 (58.1-98.3) (µmol/L)	0.043
Tyrosine 3rd Months	45.8 (42.1-64.8) µmol/L		Ornithine 3rd month	94.65 (57.7-96.5) (µmol/L)	
Tyrosine 6th Months	50.2 (49.0-59.1) µmol/L		Ornithine 6th month	104.0 (92.4-106.0) (µmol/L)	
Tyrosine 12th Months	52.4 (48.0-57.0) µmol/L	-	Ornithine 12th month	-	-
Ornithine 0th Month	77.5 (55.4-97.7) µmol/L	0.011	Aspartic acid 0th month	4.3 (3.0-6.4) (µmol/L)	0.043
Ornithine 3rd Months	62.0 (51.0-103.3) µmol/L		Aspartic acid 3rd month	6.0 (5.0-7.9) (µmol/L)	
Ornithine 6th Months	104.7 (84.5-155.0) µmol/L		Aspartic acid 6th month	7.0 (6.2-9.2) (µmol/L)	
Ornithine 12th Months	117.9 (95.8-156.4) µmol/L	-	Aspartic acid 12th month	-	-

*Friedman p (0 vs. 6th); **Wilcoxon test (0 vs. 6th).

Table II: Comparison of all amino acids in all patients according to baseline levels.

	0th month	3rd months	6th months	12th months	p1	p2	p3
	Avg±S.D/ Median (IQR)	Avg±S.D / Median (IQR)	Avg±S.D / Median (IQR)	Avg±S.D / Median (IQR)			
Glycine (µmol/L)	109.7±127.9/ 83 (63.4-100.8)	91.3±50.2/ 71.5 (67.4-94.8)	103.59±55.18/ 86.2 (70.4-109)	87.13±55.54/ 78.6 (53.8-88)	0.533	0.983	0.807
Alanine (µmol/L)*	189.7±182.2/ 134.2 (109.1-214)	202.13±140.65/ 146.5 (113.3-242.6)	233.83±166.6/ 168 (136.4-266.57)	225.53±98.56/ 219.8 (140.2-275)	0.838	0.086	0.158
Alpha amino butyridine(µmol/L)	189±128.8/ 171.7 (137.4-222.6)	198.56±63.46/ 204.8 (153.6-244.1)	244.76±103.63/ 222.55 (192.7-241)	226.12±70.49/ 238 (191.1-255)	0.378	0.776	0.084
Serine (µmol/L)	120.9±98.7/ 99 (79.3-129.9)	118.49±60.95/ 104.2 (66.9-144.5)	123.4±67.48/ 105.7 (74.5-144)	96.79±29.38/ 102.4 (81.4-116)	0.465	0.5	0.064
Proline(µmol/L)	55.8±40.3/ 46.7 (29.7-63.4)	59.66±51.47/ 44.8 (28.9-74.5)	73.13±63.4/ 48.85 (36.7-98.9)	79.36±77.55/ 48.7 (29-68.9)	0.584	0.248	0.101
Valine(µmol/L)	70.2±97.2/ 51.8 (40.9-74)	65.05±28.79/ 59 (46.84-74.8)	69.85±34.6/ 60.95 (47-71.2)	70.5±35.2/ 62 (52.5-82.4)	0.627	0.157	0.059
Threonine (µmol/L)	106.75±120.79/ 91.1 (70.1-113)	105.21±30.78/ 103.2 (91.3-123.4)	117.3±37.05/ 111.75 (102-129.4)	101.9±32.3/ 108 (100-112)	0.808	0.42	0.279
Taurine(µmol/L)	41.6±23.1/ 35 (26.8-50)	48.29±23.48/ 44 (31.1-72.1)	47.73±19.07/ 42.25 (38-64)	50.39±24.6/ 48 (37.57-60)	0.808	0.248	0.422
Isoleucine (µmol/L)	9.5±17.3/ 4.5 (2.9-6.2)	6.23±2.6/ 5.6 (4.1-7.9)	6.69±2.33/ 6.89 (5-8.4)	5.95±3.03/ 4.8 (4.6-6.9)	0.301	0.327	0.311
Leucine(µmol/L)*	376.3±160.2/ 375 (280.8-467)	441.34±187.18/ 448.7 (289.2-550.8)	524.3±214.5/ 536 (445-624.8)	482.84±194.79/ 481 (423.1-654)	0.479	0.188	0.898
Asparagine (µmol/L)*	80.1±131.1/ 58.9 (38-84.1)	68.19±21.79/ 76.1 (46.4-87.3)	77.87±37.06/ 70.7 (53.1-91.4)	72.2±33.1/ 71.8 (49-93)	0.364	0.654	0.295
Aspartic Acid (µmol/L)	30.9±66.7/ 19.2 (11.9-27.6)	22.88±14.71/ 19.1 (14.9-27.2)	24.37±16.71/ 18.45 (16.4-25.4)	21.34±14.05/ 19.5 (14.5-23.6)	0.235	0.133	0.6
Glutamine (µmol/L)	62.9±76.5/ 51.4 (41.1-65.4)	63.03±23.57/ 60.4 (45.7-73.6)	74.27±25.29/ 69.2 (60.35-91.6)	69.46±23.84/ 73 (52.6-82.5)	0.171	0.012	0.116
Glutamic acid (µmol/L)	87.8±96.4/ 67.8 (54.3-89)	76.83±26.8/ 74.9 (61.5-94.6)	75.65±32.04/ 66.3 (57.8-95.4)	76.58±39.17/ 66 (57.28-92)	0.574	0.647	0.221
Methionine (µmol/L)	75.1±146.9/ 47.2 (25.2-67.9)	72.24±54.88/ 54.4 (25-106.5)	77.05±35.25/ 65.7 (58.7-79.6)	86.26±42.72/ 80 (66.4-84.5)	0.749	0.913	0.075
Histidine (µmol/L)	21.79±16.63/ 17.8 (12.4-24.8)	36.76±23.27/ 33.8 (19-50.1)	44.43±21.37/ 38.75 (30.5-49.8)	47.41±19.74/ 43.21 (32.2-58.4)	0.024	0.018	0.087
Phenylalanine (µmol/L)	45.5±13.4/ 44.7 (36.5-56.1)	58.42±21.42/ 52.2 (44-68.4)	63.76±36.43/ 53 (49-59.1)	56.07±24.2/ 52.4 (48-57)	0.988	0.811	0.917
Arginine (µmol/L)	33.6±25.1/ 30.5 (20.4-38.9)	33.97±10.15/ 36.9 (23.6-42.3)	39.59±11.57/ 39.6 (38-49.23)	38.7±9.9/ 42.1 (37.6-42.5)	0.761	0.145	0.196
Citrulline(µmol/L)	82.3±36.3/ 81.4 (56.4-98.3)	93.68±63.45/ 90.1 (53.99-103.3)	108.8±43.07/ 104.35 (84.5-138.2)	127.07±49.26/ 117.9 (95.83-156.4)	0.003	<0.001	0.002
Tyrosine (µmol/L)	165.4±132.3/ 132.4 (105.4-158)	175.36±87.14/ 149.8 (107.7-231.2)	172.85±55.65/ 148.8 (137.8-194.5)	162.27±34.95/ 162.4 (139.81-188)	0.026	0.02	0.064
Tryptophan (µmol/L)	0.2±0.2/ 0.1 (0.1-0.1)	0.2±0.3/ 0.1 (0.1-0.1)	0.1±0.1/ 0.1 (0.1-0.1)	0.1±0.1/ 0.1 (0.1-0.1)	0.976	0.327	0.152
Ornithine (µmol/L)	12.2±5.5/ 0 (0-5)	15.7±3.9/ 8 (0-12)	18.1±3.5/ 8 (5-10)	20.3±3.6/ 10 (8-14)	0.326	0.010	0.011
Lysine (µmol/L)	2±1/ 3 (2-3)	1±1/ 1 (0-2)	0±1/ 0 (0-0)	0±0 / 0 (0-0)	0.429	0.112	0.173
Arginineo succinic Acid (µmol/L)	22.4±3.4/ 20 (18-23)	22.1±3.3/ 22 (20-24)	23.2±3.5/ 23 (21-25)	24.3±3.4/ 25 (22-25)	0.44	0.128	0.144

*Avg: Average, SD: Standard deviation, IQR: 25th percentile-75th percentile. Wilcoxon test, *Paired Samples t test, 1 0th month -3rd month, 2 0th month- 6th month, 3 0th month -12th month.*

Changes in the amino acids of all patients are summarised in Table II. The MNA scores, hand dynamometers, bed sores, albumin, C-reactive protein, iron binding capacity, ferritin, phosphorus, calcium, hemoglobin levels of the patients, who were to be fed via PEG, began to improve significantly in the 3rd month; and this positive state continued in the 6th and 12th months. Parameters such as upper arm circumference, calf circumference, weight, BMI, get up and go test and iron began to increase on the 6th month.

The histidine and tyrosine levels of the patients increased in the 3rd and 6th months compared to the baseline levels. Citrulline levels tended to increase compared to baseline levels at all three visits. Ornithine levels tended to increase in the 6th and 12th months compared to the baseline levels.

DISCUSSION

In the present study, the effect of PEG on serum amino acid levels in malnourished patients was investigated. This study is valuable because it is the first study to investigate the effect of feeding with PEG on survival and serum quantitative amino acid levels.

There was a significant difference in citrulline, ornithine and tyrosine levels between visits of 13 patients who survived. In patients who died, threonine, aspartic acid and ornithine levels were also found to be significantly increased. Muscle tissue is an important organ that performs protein storage, glucose regulation, hormone production and other cellular mechanisms.[10] Malnutrition is defined as a syndrome characterised by generalised and progressive loss of muscle mass and strength, which can lead to poor outcomes such as physical disability, poor quality of life and death.[11]

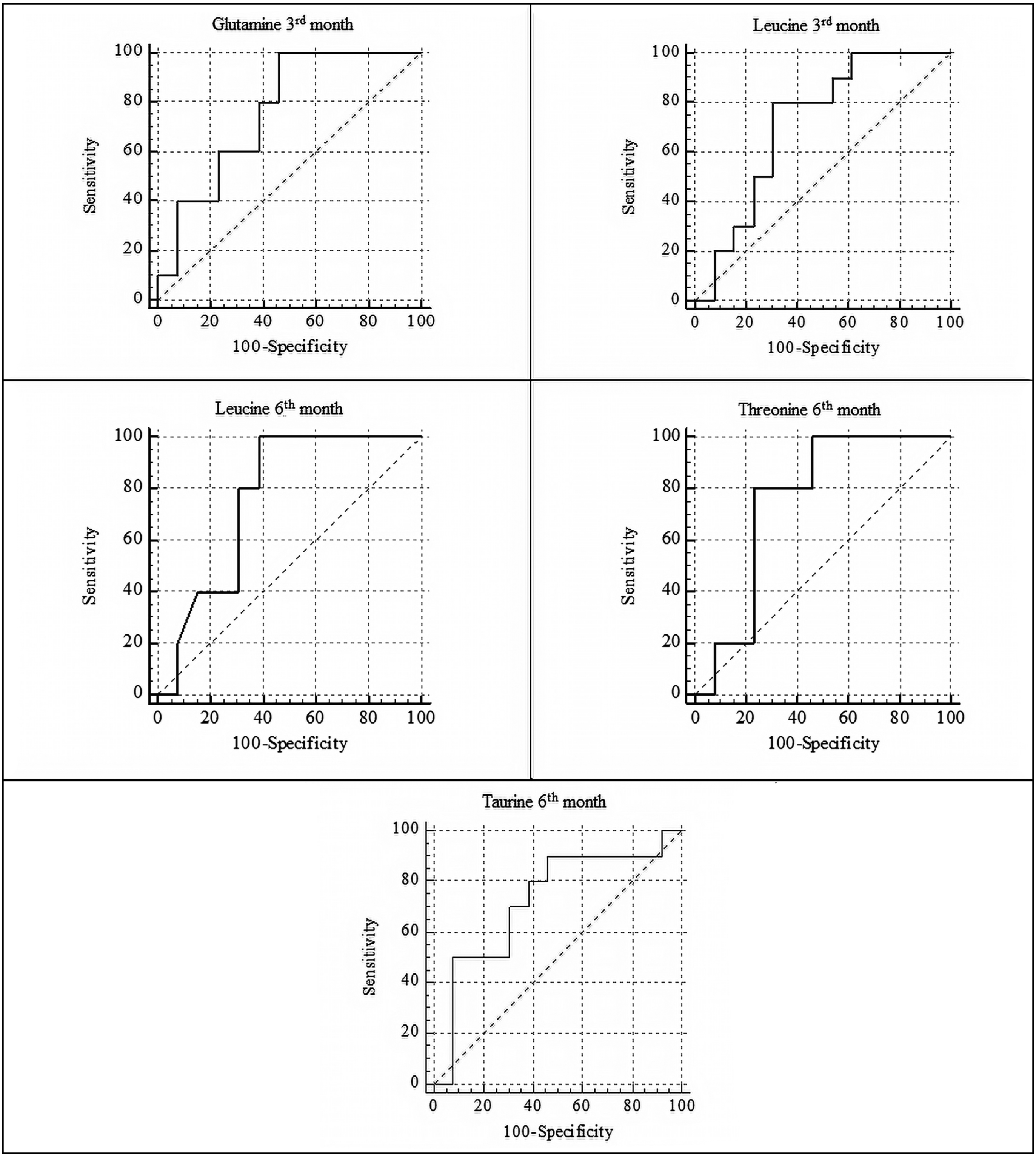

Figure 1: Significant amino acids in ROC analysis.

The pathophysiology of malnutrition is complicated in the elderly.[12] If this pathological process involving many mechanisms is not treated immediately, muscle degeneration and impaired immune response may delay healing and increase mortality. Therefore, detection of these metabolic disorders is important for clinical management in these patients.

There are variable data in the literature about the life expectancy of patients fed with PEG. The first death occurred on day 2 and the last death occurred on day 318 during the present study period. The survival time of the 13 patients was also more than 365 days. The lack of any study on the effect of quantitative amino acid levels on life expectancy, malnutrition, physical performance, and muscle strength in these patients makes this study very important.

Feeding with PEG is the most effective and safest option to feed patients with a normal digestive system, but with reduced swallowing reflex.[13] In this study, as in the study by Erdil *et al.,* nutritional parameters rapidly improve in patients fed by PEG.[14]

In the present study, concentration of some amino acids was found to be increased, some fluctuated, and most of them did not change. In a study conducted in critically ill patients in the intensive care unit, sulfur-containing amino acids, especially taurine, were found to be lower in patients with severe sepsis.[7] However, in the present study, there was no association between taurine levels with survival or mortality. In the same study, the concentrations of arginine, glutamine, phenylalanine, taurine, aspartic acid, ethanolamine, homocysteine, and glutamic acid were found to be significantly higher in sepsis patients.[7] In the present study, a significant increase in threonine, aspartic acid and ornithine levels was found close to the time of death in patients who died. These results show that aspartic acid may be an indicator of mortality in patients with severe metabolic problems due to malnutrition. In another study, lower levels of leucine, isoleucine, and valine have been shown to promote protein catabolism and decrease muscle protein synthesis.[15] However, in the present study, these amino acids were not associated with either survival or mortality.

The levels of citrulline, ornithine, and tyrosine increased gradually in 13 patients who survived in the present study. Supplementation of these amino acids in these patients may contribute positively to mortality. A study in critically ill patients showed that consumption of proline, histidine, and the ornithine increased, but levels of arginine, glutamine, and glutamic acid remained high. This balance plays an important role in the regulation of acid / base homeostasis, fibroblast, lymphocyte and enterocyte growth and the total amount of protein in the skeletal muscle.[16] In the present study, ornithine level was increased gradually both in patients who survived and in patients who died. This study was in contradiction with the current data in the literature on this subject.

Citrulline is associated with gastrointestinal system disorders.[17] In this study, the authors found that the citrulline levels of surviving patients gradually increased due to active use of the gastrointestinal tract after PEG. Citrulline has been shown to improve vascular function, reduce blood pressure and increase peripheral blood flow by increasing the synthesis of nitric oxide. This situation increases oxygenation of peripheral muscle tissue and causes an increase in muscle function and strength.[18] In a study conducted in infantile rats, it was shown that citrulline supplementation increased the interleukin-10 level by increasing the production of interferon-gamma, which in turn affected functions of the T-regulator cell.[19] Citrulline level also increased significantly in patients who survived in this study. This significant effect of the citrulline level on the survivors of the patients can be explained by the increase in peripheral oxygenation and regulation of the immune system.

Tyrosine is a semi-essential amino acid in humans. It is synthesised from phenylalanine by adding a hydroxyl group to the aromatic ring.[20] *In vivo,* tyrosine plays an important role in the synthesis of catecholamine, thyroxine, dopamine, norepinephrine and epinephrine and melanin. Tyrosine is an essential amino acid that easily crosses the blood-brain barrier. Therefore, it is an important part of the body's sympathetic nervous system.[21] People who are under stress need more tyrosine. Tyrosine supplementation in these individuals increases the resistance of the metabolism against stress by preventing depletion of norepinephrine.[22] In this study, the tyrosine level increased significantly in patients who survived. In the present study, the positive effect of tyrosine amino acid on survival was shown. This effect is shown by increasing the endurance of the organism under stress by decreasing the consumption of epinephrine and norepinephrine in the catabolic process of our malnourished patients.

Threonine, an essential amino acid for the nervous system, also plays an important role in fat metabolism.[23] It has important functions, especially in collagen tissue.[23] In this study, threonine level increased significantly in patients who survived. This significant effect of the threonine level on both bed wounds and survivors can be explained by its regulatory role of collagen and adipose tissue.

Ornithine is known to increase liver function and help detoxification of harmful substances.[24] It is claimed that ornithine positively affects wound healing, increases physical performance and the immune system.[24] Catabolic states such as burns affect the ornithine level in tissues in the body.[25] In the present study, it was found that the level of ornithine was increased in the follow-up of both the dead and surviving patients. The authors could not explain the relationship of ornithine level with both survival and mortality.

The present study had some limitations. Amino acid levels were evaluated at four different time points. It was not a cohort study so that the authors could not establish a causal relationship between quantitative amino acid and mortality and survival.

CONCLUSION

The amino acid profiles of patients with malnutrition clearly changed. The present study results suggest a close and significant relationship between impaired energy metabolism and muscle protein degradation in severely malnourished patients. There is a close and significant relationship between impaired energy metabolism and muscle protein destruction in patients with severe malnutrition. Increased citrulline, ornithine, and tyrosine levels are noteworthy in patients who survived. This study provides a theoretical basis for nutritional support in the treatment of patients with malnutrition and PEG implantation. Additional treatments containing citrulline and tyrosine may be beneficial for recovery, but clinical randomised controlled trials are needed to confirm these results.

ETHICAL APPROVAL:

The study was approved by the Institutional Ethics Committee of University of Health Sciences, Umraniye Training and Research Hospital. (Date: 19.11.2015; Number: B.10.1.TKH.4.34.H.GP.0.01/85).

PATIENTS' CONSENT:

Informed consents were obtained from all patients / relatives before the study began.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

RS, SUB, NG: Conception and design, data acquisition, data analysis and interpretation. Manuscript drafting and critical revision of the manuscript, statistical analysis, supervision.

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