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# Plasma Amino Acid Levels in Obese Adolescents: A Case-Control Study and the Review of the Literature

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## Abstract

Optimal balance among amino acids in the circulation is important for body homeostasis. This study aims to evaluate and define the amino acids associated with obesity and insulin resistance. Fifty obese and 42 healthy adolescents aged 10-18 years were included in this study. Fasting plasma glucose, liver enzymes, thyroid function tests, insulin, and lipid levels were studied as routine laboratory examinations, and 26 plasma amino acids were studied as specific laboratory examinations. Isoleucine, leucine, lysine, tryptophan, glutamate, tyrosine, phenylalanine, alanine, methionine, argininosuccinic acid, histidine and valine were significantly higher in patients with obesity. Asparagine and citrulline levels were lower in patients with insulin resistance. The metabolic pathways of various amino acids are significantly impaired in obesity. Plasma concentrations of essential, non-essential, branched-chain, and aromatic amino acids were elevated in this study.

**Keywords:** Amino acids, adolescent, obesity

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## Introduction

Obesity has emerged as a global health issue affecting both children and adults. It increases the likelihood of developing metabolic disorders, including insulin resistance, type 2 diabetes, elevated uric acid levels, abnormal lipid profiles, high blood pressure, and non-alcoholic fatty liver disease. Metabolic complications associated with obesity are important because they cause mortality and morbidity. Understanding the mechanisms could help to identify therapeutic strategies[1,2].

**Highlights**

- Optimal balance among amino acids in the circulation is important for body homeostasis.
- The metabolic pathways of various amino acids are significantly impaired in obesity.
- Plasma concentrations of essential, non-essential, branched-chain and aromatic amino acids were found to be elevated in our study.

Amino acids (AAs), which contain both an amino and a carboxyl group, undergo metabolic processes that result in the formation of several compounds, including ammonia, fatty acids, glucose, ketone bodies, urea, uric acid, and polyamines. These metabolites take part in various cycles such as the tricarboxylic acid (TCA) and urea cycle, and vital functions such as gluconeogenesis, ketogenesis, acid -base balance, and the synthesis of nucleotides and lipids. Deficiency or excess in plasma AA occurs when these pathways are disrupted. Increased concentrations of AAs and their products can contribute to oxidative stress and associated poor metabolic conditions. Maintaining an appropriate balance of AAs in both the diet and bloodstream is essential for preserving physiological homeostasis[3].

The mechanisms by which AAs contribute to insulin resistance are complex, and studies have been particularly focused on branched-chain amino acids (BCAAs). Leucine is a potent activator of the mammalian target of rapamycin complex 1 (mTORC1). Chronic mTORC1 activation disrupts insulin signaling by enhancing the serine phosphorylation of insulin receptor substrate-1. As a result, cells become less responsive to insulin, leading to insulin resistance**.** In addition, incomplete catabolism of BCAAs results in the accumulation of toxic metabolic intermediates, which can impair mitochondrial function, activate stress-responsive kinases, and promote β-cell dysfunction. Specific BCAA-derived metabolites, such as 3-hydroxyisobutyrate and acetyl-CoA, interfere with fatty acid β-oxidation, leading to the intracellular accumulation of lipids like diacylglycerol and ceramides in skeletal muscle. These lipids activate protein kinases, impair insulin signaling, and exacerbate insulin resistance[4-7].

There are relatively few studies evaluating AA levels in childhood obesity. Butte et al.[8] reported that BCAAs and AAs such as alanine, glutamate, lysine, phenylalanine, and tyrosine were elevated in obese children. McCormack et al.[9] showed that elevations in the concentrations of BCAAs were significantly associated with BMI Z-score and homeostatic model assessment for insulin resistance (HOMA-IR). Elshorbagy et al.[10] demonstrated that total cysteine concentrations are independently related to obesity and insulin resistance. Zhao et al.[11] reported that BCAAs and aromatic AAs were closely related to insulin resistance and future metabolic risk.

The primary objective of this study was to define AAs associated with obesity and insulin resistance. We hypothesized that some AA changes may be biomarkers for metabolic decompensation and could be used in the treatment of childhood obesity.

## Material and Method

### Study Design

Our study was planned as a case-control prospective observational study.Adolescents with obesity who were evaluated in the pediatric metabolism and endocrinology clinics of the Kayseri Erciyes Training and Research Hospital between November 2017 and May 2018, were included in the study.

### Inclusion Criteria

### Patient Group

The obesity group consisted of 50 patients aged 10 to 18 years, all with a body mass index (BMI) greater than the 95$^{th}$ percentile and a BMI Z-score above 2. BMI Z-scores were determined using the World Health Organization's data[12]. None of the patients were on a diet and/or exercise. There was no infection or catabolic condition that could affect plasma AAs according to physical examination findings and laboratory results.

### Control Group

The control group was selected, consisting of gender and age-matched, completely healthy adolescents with BMI below the 85$^{th}$ percentile, chosen from pediatric policlinics for a check-up or for preoperative evaluation of minor elective surgery. Simple random sampling was used for all subject choices.

### Exclusion Criteria

Patients with primary hyperlipidemia, primary liver disease, and secondary obesity were excluded.

### Measurements

The height and weight were measured using an automatic device (G-TECH, GL-150). BMI was obtained by dividing the individual's body weight in kilograms by the square of their height, measured in meters (kg/m$^2$). HOMA-IR was used to determine the IR. HOMA-IR was calculated by multiplying fasting blood glucose (milligrams/dl) by insulin (milliunits/milliliter) and dividing it by 405. A value above 3.16 was accepted as IR[13].

### Analyses

All samples were collected after a 12-hour overnight fast. Plasma glucose, liver enzymes, thyroid function tests, insulin, and lipid levels were studied as routine laboratory examinations.

Glucose, triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein were measured

by spectrophotometric methods using an automated clinical chemistry analyzer (C702, Roche Diagnostics, Mannheim, Germany).

Insulin, T4 and thyroid-stimulating hormone levels were measured by electrochemiluminescence assay (E601, Roche Diagnostics, Mannheim, Germany).

A two-milliliter blood sample was taken in a fasting state into EDTA tubes, kept at +4 °C for 15 minutes, and centrifuged at 3500 rpm for 15 minutes in order to study plasma AA levels. All samples were preserved at -80 °C until analysis. Plasma AAs were measured by using Zivak Tandem Gold LC-MS/MS system, in the pediatric metabolism laboratory of Erciyes University Faculty of Medicine. A total of 26 AAs: Alanine, arginine, argininosuccinic acid, asparagine, aspartic acid, cysteine, citrulline, glutamine, glutamate, glycine, homocysteine, hydroxylysine, hydroxyproline, isoleucine, leucine, lysine, methionine, ornithine, proline, serine, threonine, tryptophan, tyrosine, phenylalanine, valine, and histidine were studied.

### Ethical Approval

Ethical approval was received from the Ethics Committee of Erciyes University Faculty of Medicine (approval no: 487/2017, date: 27.10.2017).

### Statistical Analysis

Statistics were analyzed using SPSS version 26. Data with a normal distribution were presented as mean, ± standard deviation, while non-normally distributed variables were expressed as median and interquartile range ($25^{th}$-$75^{th}$ percentile). For comparisons between two groups, the independent samples t-test was used for normally distributed variables, and the Mann-Whitney U test was applied to non-parametric data. Categorical variables were analyzed using the chi-square test. Spearman's correlation was employed to evaluate relationships between non-parametric variables. Multiple linear regression analysis of the association of AAs with BMI change was used to identify the AAs associated with obesity. A p-value of less than 0.05 was indicative of statistical significance throughout all analyses.

## Results

The study consisted of 50 (23 M/27 F) adolescents with obesity and 42 (16 M/26 F) healthy controls. The mean ages of the obese group were 13.4±2.0 years and of the healthy controls were 13.7±2.0 years. The AAs: isoleucine, leucine, lysine, tryptophan, tyrosine, phenylalanine, alanine, methionine, glutamate, argininosuccinic acid, histidine, and valine were significantly higher in the obese group than healthy controls. Only glycine levels were lower in the obese group. Comparison of the variables between the obese and control groups is shown in **Table 1**.

Alanine, glutamate, methionine, phenylalanine, isoleucine, leucine, valine, tyrosine, tryptophan, proline, and lysine levels were positively correlated; serine and glycine levels were negatively correlated with obesity-related parameters. Correlation of AAs with obesity related parameters is shown in **Table 2**.

The relationship between AAs that may influence BMI changes was examined with a multivariate linear regression model. We did not observe any autocorrelation, and there was no multicollinearity problem. Alanine, glutamate, glycine, isoleucine, and valine levels were statistically significantly associated with BMI change. The results of multiple linear regression analysis relating AAs to BMI are shown in **Table 3**.

Twenty-eight percent of adolescents with obesity had IR. The mean age was 13.6±2.2 in the group with IR and 13.0±1.8 in individuals without IR. The asparagine and citrulline levels were lower in individuals with IR. Comparison of the variables between two obese groups is shown in **Table 4**.

## Discussion

The relationships between obesity, IR, diabetes, cardiovascular diseases, and plasma AAs have been shown in various studies for adults[14-16]. There are relatively few studies evaluating AAs in adolescents with obesity.

BCAAs represent around 20% of the body's protein composition and comprise one-third of the essential AAs. Butte et al.[8] and Ye et al.[6], reported that BCAAs were significantly increased in children with obesity. Similar to previous studies, our research revealed that plasma BCAA levels were elevated in children and adolescents with obesity.

BCAAs have been shown to contribute to early diagnosis, and they can be used as a biomarker to show complications that may develop in obesity[7,17,18]. Although previous studies[19-22] have established a connection between BCAAs and IR, our findings did not show any difference in BCAA levels between obese adolescents with or without IR.

This can be explained by the small number of patients due to the fact that the HOMA-IR value is taken as (3.16). Bi et al.[15] reported that they did not observe any difference in BCAAs between patients with or without IR, as observed in our study.

Phenylalanine is an essential aromatic AA that has an effect on BH4 activation, tyrosine synthesis and neurological development[3]. Bi et al.[15] reported that the increase in phenylalanine, tyrosine, methionine, and alanine was strongly associated with hyperinsulinemia. Similarly, when comparing plasma alanine, tyrosine, methionine, and phenylalanine levels in our patients with obesity to healthy controls, these levels were found to be high, but there was no difference in these AAs between individuals with or without IR.

Glutamate is a non-essential AA that acts as a bridge between urea and TCA cycles. After the increase in plasma glutamate, genes related to the TCA cycle are downregulated, and gluconeogenesis is increased with increased levels of glucagon, and pyruvate is converted to alanine. Glucose levels increase as a result[3]. Glutamate levels weren't associated with IR in our study.

Glycine is a non-essential AA and is involved in the synthesis of glutathione, purine, serine, and porphyrins.

**Table 1.**
*Comparison of the variables between obese and control group*

| Variable | | Obese group (n=50) | Control group (n=42) | p |
|---|---|---|---|---|
| **Gender (F/M)** | n | (27/23) | (26/16) | **0.445**$^{x2}$ |
| **Age (years)** | Mean ± SD | 13.4±2.0 | 13.7±2.0 | **0.515**$^{t}$ |
| **Weight (kg)** | Mean ± SD | 79.0±19.6 | 48.8±12.6 | **0.000** $^{t}$ |
| **BMI (kg/m$^2$)** | Median (25-75p) | 30.6 (27.7-33.7) | 20.0 (17.7-22.2) | **0.000**$^{m}$ |
| **Insulin (mu/L)** | Median (25-75p) | 15.5 (9.2-25.2) | 10.5 (8.1-12.5) | **0.000**$^{m}$ |
| **HOMA-IR** | Median (25-75p) | 3.3 (2.3-5.8) | 2.5 (1.8-2.8) | **0.000**$^{m}$ |
| **BMI Z-score** | Median (25-75p) | 2.85 (2.4-3.2) | 0.05 (0.3-0.9) | **0.000**$^{m}$ |
| **ALT (U/L)** | Median (25-75p) | 23.0 (18.0-31.5) | 15.0 (12.0-18.2) | **0.000**$^{m}$ |
| **HDL (mg/dL)** | Mean ± SD | 43.8±8.1 | 47.3±3.5 | **0.008**$^{t}$ |
| **Alanine** | Median (25-75p) | 437.5 (379.7-502.1) | 379.1 (306.7-455.8) | **0.002**$^{m}$ |
| **Glutamate** | Median (25-75p) | 25.1 (15.8-120.1) | 17.5 (12.5-65.2) | **0.009**$^{m}$ |
| **Glycine** | Median (25-75p) | 228.5 (205.2-259.4) | 252.3 (230.6-306.0) | **0.007**$^{m}$ |
| **Methionine** | Mean ± SD | 32.1±8.3 | 28.8±7.1 | **0.047**$^{t}$ |
| **Isoleucine** | Mean ± SD | 78.9±20,4 | 64.3±17.2 | **0.000**$^{t}$ |
| **Leucine** | Mean ± SD | 154.5±33.7 | 122.1±26.9 | **0.000**$^{t}$ |
| **Tyrosine** | Mean ± SD | 81.7±20.0 | 65.2±16.2 | **0.000**$^{t}$ |
| **Valine** | Mean ± SD | 280.8±59.9 | 212.5±49.8 | **0.000** $^{t}$ |
| **ASA** | Median (25-75p) | 0.20 (0.05-0.5) | 0.08 (0.01-0.3) | **0.013**$^{m}$ |
| **Lysine** | Median (25-75p) | 178.2 (155.8-200.3) | 148.7 (132.1-175.4) | **0.000**$^{m}$ |
| **Phenylalanine** | Median (25-75p) | 73.5 (60.2-86.3) | 63.9 (54.2-70.8) | **0.002**$^{m}$ |
| **Tryptophan** | Mean ± SD | 46.7±10.7 | 39.2±10.2 | **0.001**$^{t}$ |
| **Histidine** | Median (25-75p) | 91.5 (82.8-102.4) | 82.7 (77.4-93.7) | **0.018**$^{m}$ |

$^{m}$; Mann-Whitney U test/$^{t}$; Independent samples-2 test/$^{x2}$; Chi-square test
ASA; Argininosuccinic acid, SD; Standard deviation, BMI; Body mass index, ALT; Alanine aminotransferase, HOMA-IR; Homeostatic model assessment for insulin resistance, HDL; High-density lipoprotein, F; Female, M; Male

This indicates that the human body can synthesize the required glycine internally through *de novo* synthesis. Low plasma glycine levels have been associated with obesity, type 2 diabetes, and non-alcoholic fatty liver disease[23]. Guevara-Cruz et al.[24] showed that plasma alanine, asparagine, proline, and tyrosine increased while glycine levels decreased in patients with obesity. Okekunle et al.[25] showed that isoleucine, valine, glutamate and proline increased, and glycine decreased in patients with obesity and diabetes. Similar to previous studies, we observed a reduction in plasma glycine levels in adolescents with obesity compared to healthy controls.

Xu et al.[26] demonstrated that asparagine enhances mTORC1 signaling, thereby promoting glycolysis in adipose tissue. They showed that dietary supplementation with asparagine led to marked reductions in serum insulin and triglyceride levels, suggesting improved systemic regulation of glucose and lipid metabolism. Also, Tosur et al.[27] showed that pediatric type 2 diabetes patients had lower arginine, citrulline, glutamine, glycine, phenylalanine, methionine, threonine, and asparagine levels than those with type 1 diabetes. Bugajska et al.[28] reported that plasma levels of leucine, isoleucine, valine, phenylalanine, tyrosine, glutamic acid, and alanine were significantly higher and that the mean values of serine, asparagine, glutamine, and citrulline were significantly lower in overweight and obese children. Our findings showed that plasma asparagine and citrulline concentrations remained normal in obese adolescents, but they were reduced in those exhibiting insulin resistance. Reduced asparagine and citrulline levels may serve as early indicators of an increased risk for developing type 2 diabetes mellitus.

Hellmuth et al.[29] conducted a study involving 80 obese children who participated in a one-year lifestyle intervention program**.** The program led to a substantial weight loss, defined as a reduction of more than 0.5 BMI standard deviation scores in 40 of the children. Among the metabolites analyzed, only tyrosine showed a significant association with insulin resistance at baseline and after the intervention.

**Table 2.**
*Correlation of amino acids with obesity-related parameters*

| | | Weight | BMI | HOMA-IR | BMI Z-score |
|---|---|---|---|---|---|
| **Alanine** | ro<br>p | 0.268<br>0.01 | 0.267<br>0.01 | 0.274<br>0.008 | 0.243<br>0.02 |
| **Glutamate** | ro<br>p | - | 0.214<br>0.041 | - | 0.255<br>0.014 |
| **Glycine** | ro<br>p | -0.208<br>0.047 | -0.294<br>0.004 | -0.230<br>0.028 | -0.348<br>0.001 |
| **Methionine** | ro<br>p | 0.223<br>0.032 | - | 0.222<br>0.034 | - |
| **Phenylalanine** | ro<br>p | 0.241<br>0.021 | 0.219<br>0.036 | - | - |
| **Isoleucine** | ro<br>p | 0.287<br>0.005 | 0.283<br>0.006 | 0.234<br>0.02 | 0.266<br>0.01 |
| **Leucine** | ro<br>p | 0.289<br>0.005 | 0.312<br>0.002 | 0.207<br>0.048 | 0.330<br>0.001 |
| **Lysine** | ro<br>p | 0.345<br>0.001 | 0.355<br>0.001 | 0.272<br>0.009 | 0.360<br>0.000 |
| **Proline** | ro<br>p | 0.242<br>0.02 | - | 0.282<br>0.006 | - |
| **Serine** | ro<br>p | - | -0.257<br>0.013 | - | -0.310<br>0.003 |
| **Tryptophan** | ro<br>p | 0.266<br>0.01 | 0.261<br>0.012 | 0.239<br>0.022 | 0.254<br>0.015 |
| **Tyrosine** | ro<br>p | 0.256<br>0.014 | 0.334<br>0.001 | - | 0.348<br>0.001 |
| **Valine** | ro<br>p | 0.354<br>0.001 | 0.412<br>0.000 | 0.269<br>0.01 | 0.425<br>0.000 |

BMI; Body mass index, HOMA-IR; Homeostatic model assessment for insulin resistance

**Table 3.**
*The results of multiple linear regression analysis of amino acids with BMI*

| | Unstandardized coefficients | | Standardized coefficients | | 95% confidence interval for B | | p value |
|---|---|---|---|---|---|---|---|
| | B | Standard error | β | t | Lower Limit | Upper Limit | |
| Constant | 18.501 | 3.460 | | 5.347 | 11.620 | 25.381 | 0.000 |
| Alanine | 0.019 | 0.009 | 0.292 | 2.124 | 0.001 | 0.037 | **0.037** |
| Glutamate | 0.025 | 0.012 | 0.186 | 2.023 | 0.000 | 0.049 | **0.046** |
| Glycine | -0.039 | 0.010 | -0.413 | -3.742 | -0.060 | -0.018 | **0.000** |
| Methionine | 0.141 | 0.128 | 0.151 | 1.106 | -0.113 | 0.395 | 0.272 |
| Phenylalanine | -0.014 | 0.041 | -0.041 | -0.344 | -0.096 | 0.068 | 0.732 |
| Valine | 0.064 | 0.021 | 0.555 | 3.040 | 0.022 | 0.105 | **0.003** |
| Isoleucine | -0.148 | 0.063 | -0.402 | -2.345 | -0.273 | -0.022 | **0.021** |

BMI; Body mass index
The relationship between amino acids that may affect the change in BMI was examined with a multivariate linear regression model. The Durbin Watson value was determined as 1.857. We observed any autocorrelation. The condition index value 27.7 and the VIF value was 1.604. We observed that there was no multicollinearity problem. The regression model was statistically significant, R=0.601, $R^2$=0.361 Adjusted $R^2$=0.308, F=(7-84)=6.783 p<0.001. A p value below 0.05 was considered statistically significant.

Lee et al.[30] reported that children with BCAA concentrations above the median at baseline exhibited an approximately threefold higher risk of developing insulin resistance and metabolic syndrome during a two-year follow-up.

In conclusion, the metabolic pathways of various AAs are significantly impaired in obesity. Isoleucine, leucine, lysine, tryptophan, tyrosine, phenylalanine, alanine, methionine, argininosuccinic acid, histidine, and valine were significantly higher in patients with obesity than healthy controls in our study. The metabolism of people with obesity is affected by many factors. There is little information about the causes, and there is a need for more studies on metabolomics of obesity in adolescents.

### Study Limitations

Our study does not include longitudinal data on plasma AAs. This restricts our ability to track the progression of metabolic changes related to obesity over time. Various studies have applied different cut-off values for HOMA-IR. Factors like age, gender, and pubertal stage play a role in determining insulin resistance. Plasma AA levels are also influenced by the nutritional habits of the individuals. However, our study does not include the nutritional habits of the participants.

**Table 4.**
*Comparison of the variables between two obese groups*

| Variable | | Insulin resistance | Without insulin resistance | p |
|---|---|---|---|---|
| **Gender (F/M)** | n | (16/12) | (11/11) | 0.615$^{x2}$ |
| **Age (years)** | Mean ± SD | 13.6±2.2 | 13.0±1.8 | 0.293$^{t}$ |
| **Weight (kg)** | Mean ± SD | 84.3±21.6 | 72.3±14.6 | **0.031**$^{t}$ |
| **BMI (kg/m$^2$)** | Median (25-75p) | 32.0 (28.2-35.2) | 29.1 (27.5-31.4) | 0.068$^{m}$ |
| **Insulin (mu/L)** | Median (25-75p) | 21.9 (17.6-33.4) | 9.1 (6.9-12.4) | **0.000**$^{m}$ |
| **HOMA-IR** | Median (25-75p) | 5.2 (3.6-8.4) | 2.0 (1.4-2.7) | **0.000**$^{m}$ |
| **BMI Z-score** | Mean ± SD | 3.0±0.8 | 2.7±0.4 | 0.068$^{t}$ |
| **ALT (U/L)** | Median (25-75p) | 25.0 (18.2-38.2) | 21.5 (17.7-28.2) | 0.538$^{m}$ |
| **HDL (mg/dL)** | Mean ± SD | 42.7±6.4 | 45.3±9.9 | 0.270$^{t}$ |
| **Alanine** | Median (25-75p) | 446.5 (417.2-574.7) | 419.7 (366.2-481.8) | 0.197$^{m}$ |
| **Methionine** | Mean ± SD | 32.7±8.6 | 31.4±8.2 | 0.588$^{t}$ |
| **Isoleucine** | Mean ± SD | 81.1±23.1 | 76.2±16.4 | 0.413$^{t}$ |
| **Leucine** | Mean ± SD | 158.0±37.0 | 150.0±29.2 | 0.413$^{t}$ |
| **Tyrosine** | Mean ± SD | 83.4±22.9 | 79.6±15.9 | 0.508$^{t}$ |
| **Valine** | Mean ± SD | 290.3±68.9 | 268.7±44.6 | 0.186$^{t}$ |
| **Asparagine** | Mean ± SD | 60.4±16.7 | 71.1±19.7 | **0.045**$^{t}$ |
| **Lysine** | Median (25-75p) | 183.9 (159.0-204.2) | 171.2 (154.9-199.2) | 0.538$^{m}$ |
| **Phenylalanine** | Median (25-75p) | 75.6 (60.7-86.9) | 71.4 (59.1-80.6) | 0.379$^{m}$ |
| **Tryptophan** | Median (25-75p) | 49.5 (38.8-55.7) | 44.7 (38.2-48.9) | 0.171$^{m}$ |
| **Citrulline** | Median (25-75p) | 21.2 (17.5-26.5) | 27.3 (22.2-39.8) | **0.043**$^{m}$ |

$^{m}$; Mann-Whitney U test/$^{t}$; Independent samples-2 test/$^{x2}$; Chi-square test
SD; Standard deviation, BMI; Body mass index, ALT; Alanine aminotransferase, HOMA-IR; Homeostatic model assessment for insulin resistance, HDL; High-density lipoprotein, F; Female, M; Male

## Ethics

**Ethics Committee Approval:** Ethical approval was received from the Ethics Committee of Erciyes University Faculty of Medicine (approval no: 487/2017, date: 27.10.2017).

**Informed Consent:** Informed consent was obtained from the parents of all patients participating in the study.

## Footnotes

Authorship Contributions: Soylu Üstkoyuncu P: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Doğan D: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search, Writing; Kardaş F: Concept, Design, Literature Search, Writing; Kendirci M: Concept, Design, Data Collection or Processing, Literature Search, Writing; Dündar MA: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Canpolat A: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Literature Search; Altuner Y: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search.

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