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ORİJİNAL ARAŞTIRMA

Amino Acid Levels in Patients with Fibromyalgia Syndrome

Fibromiyalji Sendromlu Hastalarda Amino Asit Düzeyleri

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ABSTRACT

Aim: Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterised by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive symptoms, making the patients seek long-term healthcare. While it is more common in females, the exact aetiopathogenesis of the disease is not clear, and current biomedical and psychosocial treatments are insufficient for many patients. This study aimed to examine the amino acid profile levels of patients with FMS to identify the amino acids that can potentially be used in the diagnosis and treatment of FMS.

Material and Method: Ninety participants (female patients diagnosed with FMS: n=45, mean age= 42.80±11.78 years; healthy controls: n=45, mean age=39.60±12.35 years) who applied to the Physical Medicine and Rehabilitation Clinic were recruited. Blood samples were drawn from all participants, and their plasma amino acid profiles were measured using an 8045 LC-MS/MS device. Multivariate analysis of the amino acid profile parameters was performed.

Results: The mean plasma levels of alanine, arginine, aspartic acid, citrulline, glutamine, glutamic acid, glycine, histidine, leucine, isoleucine, alloisoleucine, phenylalanine, proline, serine, tyrosine, valine, alpha aminopimelic acid, hydroxy proline, serotonin, 5-hydroxytryptamine, taurine, glutamine, and glutamic acid were significantly lower in the FMS patients group ($p < 0.001$). In contrast, tryptophan, cystine, anserine, argino succinic acid, and gamma amino butyric acid levels were significantly higher among the patients with FMS ($p < 0.001$).

Conclusion: There were obvious differences in the amino acid profiles of patients with FMS and their corresponding healthy controls. These findings indicate the role of amino acids in elucidating the pathophysiology of FMS and as potential biomarkers in its prognosis, treatment, and follow-up.

Keywords: Fibromyalgia, Amino acids, LS-MS/MS

ÖZ

Amaç: Fibromiyalji sendromu (FMS), yaygın kas-iskelet ağrısı, yorgunluk, uyku bozuklukları ve kognitif semptomlarla karakterize kronik bir ağrı sendromudur ve hastaları uzun süreli sağlık hizmeti almak zorundadır. Kadınlarda daha sık görülmekle birlikte, hastalığın kesin etiyopatogenezi net değildir ve mevcut biyomedikal ve psikososyal tedaviler birçok hasta için yetersizdir. Bu çalışmada FMS'li hastaların amino asit profil düzeylerinin incelenmesi ve FMS'nin tanı ve tedavisinde potansiyel olarak kullanılabilecek amino asitlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Fiziksel Tıp ve Rehabilitasyon Kliniği'ne başvuran doksan katılımcı (FMS tanılı kadın hastalar: n=45, ortalama yaş= 42.80±11.78 yıl; sağlıklı kontroller: n=45, ortalama yaş=39.60±12.35 yıl) çalışmaya dahil edildi. Tüm katılımcılardan kan örnekleri alındı ve plazma amino asit profilleri 8045 LC-MS/MS cihazı kullanılarak ölçüldü. Amino asit profil parametrelerinin çok değişkenli analizi yapıldı.

Bulgular: Alanin, arginin, aspartik asit, sitrülin, glutamin, glutamik asit, glisin, histidin, lösin, izolösin, alloizolösin, fenilalanin, prolin, serin, tirozin, valin, alfa aminopimelik asit, hidroksi prolin, serotonin, 5-hidroksitriptamin, taurin, glutamin ve glutamik asit ortalama plazma düzeyleri FMS hasta grubunda anlamlı olarak daha düşüktü ($p < 0.001$). Buna karşılık, triptofan, sistin, anserin, argino süksinik asit ve gama amino bütirik asit düzeyleri FMS'li hastalarda anlamlı olarak daha yüksekti ($p < 0.001$).

Sonuç: Anlamlı olan amino asitlerin FMS'nin patofizyolojisinin aydınlatılmasında; prognozu, tedavisi ve takibinde potansiyel biyobelirteç rolü olabileceğini göstermektedir.

Anahtar Kelimeler: Fibromiyalji, Amino asitler, LS-MS/MS

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic disease of unknown aetiology with symptoms affecting multiple body systems. It is typically characterised by widespread body pain and the development of tender points. Essentially, FMS is a central desensitization syndrome in which the central processing of pain is impaired (1). Patients with FMS often require symptomatic care for years (2). However, current medical and psychosocial treatments are inadequate for many patients. Due to the lack of a clear understanding of the pathophysiology of FMS, little progress has been made in the treatment options for FMS (3).

Physiologically, amino acids play a vital role in maintaining immunity, regulating redox homeostasis, and serving as substrates for protein synthesis (4, 5). Functional amino acids, including glutamine, arginine, glycine, glutamic acid, and tryptophan, improve inflammatory disorders. Lately, extensive research has been done to understand how dietary amino acids affect growth, development, and immune response in mammals (6), Which has expanded our understanding of the activity of amino acids.

Tryptophan, phenylalanine, and tyrosine are classified as aromatic amino acids due to the presence of benzyl-based aromatic groups. Apart from acting as the building blocks of proteins, aromatic amino acids are critical in the body's metabolic and immune processes (6). Consequently, disturbances in their metabolism are associated with several hereditary diseases and neurological symptoms, especially those involving damage or deficiency of a cellular enzyme.

The amino acid aspartate is a critical precursor for protein synthesis, especially in pyrimidine and purine production, and primarily functions as a neurotransmitter, apart from its role in hormone secretion, neuronal protection, and reproductive regulation (7). Blachier et al. stated that aspartate triggers metabolic reprogramming and activation of hypoxia inducible factor-1α (HIF-1α) and NOD-like receptor protein-3 (NLRP3) in peritoneal macrophages, thus causing severe pain (8). Asparagine, an aspartate derivative, triggers this cellular metabolic reprogramming and HIF-1α activation, leading to increased interleukin-1β production from M1 macrophages (8).

In this context, the current study aims to define the relationship between different amino acids and FMS to reveal the mechanisms underlying the beneficial activities of these amino acids.

MATERIAL AND METHOD

Female patients with FMS (n=45) and healthy female controls (n=45) in the same age group, not having an existing chronic disease, and not taking any medication who applied to have widespared pain the Harran University Faculty of Medicine Physical Medicine and Rehabilitation Polyclinic were included in this study. FMS diagnosis was made according to the ACR's 2010 diagnostic criteria (9). Written consent for participation was obtained from all participants. Ethical approval for the study was obtained from the Harran University Clinical Research Ethics Committee (approval number: 23/10/04; dated: 05.06.2023).

A 5-cc blood samples were taken from all participants at 08.00 AM and stored at -80°C until the time of the study. The blood was centrifuged at 4000 rpm for 10 min, and the plasma section was separated. The plasma samples were analysed using the JASEM amino acid kit at the Biochemistry Laboratory of the Harran University Faculty of Medicine Research and Application Hospital. For analysis, 45 different amino acid parameters were studied by placing them in the tray section of the HPLC section of the LC-MS/MS device (Shimadzu 8045, Japan).

Statistical Analysis

For descriptive analysis, mean±standard deviation and range were computed for numerical variables, and frequency and percentages for categorical variables. Normality of the distribution of the data was examined using the Kolmogorov-Smirnov test; accordingly, Student's t-test for normally distributed features and the Mann-Whitney U test for non-normally distributed. Relationships between categorical variables were analysed using Pearson's chi-square or Fisher's exact tests. SPSS for Windows (version 20, IBM Corp., Armonk, NY, USA) was used for statistical analysis; a p-value of <0.05 was considered statistically significant.

RESULTS

The AA's between groups data are presented in Table 1. In patients with FMS, plasma levels of free amino acids–alanine, arginine, aspartic acid, citrulline, glutamine, glutamic acid, glycine, histidine, leucine, isoleucine, allo-isoleucine, lysine, phenylalanine, proline, serine, tryptophan, tyrosine, hydroxyproline, cystine, homocysteine, serotonin, and taurine were statistically significantly lower compared to the control group (p <0.001 each).

Likewise, a statistically significant difference was found in the levels of branched chain amino acids (BCAAs) valine, leucine, and isoleucine in the patient group compared to the control group (p <0.001 each). However, there were no statistically significant differences in the plasma levels of asparagine, ornithine, methionine, and threonine between the two groups.

Table 1. The AA's between groups

	Control Group			Patient Group			p
	Min	Max	Mean±SD	Min	Max	Mean±SD	
Alanine	222.72	768.49	483.07±186.27	153.98	524.12	274.73±83.43	<0.001
Argjnine	177.19	605.43	303.61±112.90	21.32	111.12	68.49±22.42	<0.001
Asparagine	16.04	76.18	41.07±20.96	26.59	66.31	43.93±11.42	0.628
Aspartic Acid	42.33	158.22	95.67±39.24	1.21	44.62	10.49±10.83	<0.001
Citrulline	10.37	44.67	31.52±9.97	5.57	31.67	19.04±7.21	<0.001
Glutamin	161.55	709.45	348.77±147.97	66.09	312.70	139.17±65.15	<0.001
Glutamic Acit	131.56	505.25	310.92±112.74	19.76	264.65	78.31±47.00	<0.001
Glisine	148.38	419.94	306.34±77.34	116.15	340.66	198.01±50.47	<0.001
Histidine	97.92	255.56	170.51±48.14	30.69	87.42	57.52±12.48	<0.001
Leucine	101.99	381.01	220.73±85.66	20.00	149.43	95.27±27.06	<0.001
İsoleucine	54.62	195.51	120.87±45.54	10.27	91.51	59.96±15.95	<0.001
Allosoleucine	0.63	2.74	1.43±0.60	0.06	1.13	0.36±0.20	<0.001
Lysine	148.40	464.60	297.29±104.64	43.47	228.72	132.56±36.88	<0.001
Methionine	13.07	47.89	29.51±12.01	11.50	37.21	24.25±6.27	0.129
Ornithine	16.72	106.14	59.91±29.70	40.41	136.72	67.51±22.88	0.441
Phenylalanine	68.01	210.37	132.91±44.47	33.82	72.58	51.10±10.20	<0.001
Proline	147.08	646.15	318.48±144.44	101.68	249.54	155.49±40.28	<0.001
Serine	143.16	404.89	236.52±69.05	90.10	193.18	130.52±31.19	<0.001
Threonine	78.64	215.22	154.46±48.23	74.82	203.54	132.52±37.08	0.098
Tryptophan	49.22	155.76	83.72±30.58	26.15	81.56	56.44±14.93	0.002
Tyrosine	60.39	170.36	102.33±35.34	33.55	112.31	68.62±16.83	0.003
Valine	150.76	432.52	266.94±88.49	48.62	285.22	174.70±47.57	0.001
Alpha Amino Adipic Acid	0.10	2.25	1.03±0.65	0.18	2.92	0.94±0.57	0.904
Anserine	0.04	0.44	0.18±0.12	0.09	8.82	2.11±2.31	<0.001
Arginino Succinic Acid	0.02	0.44	0.10±0.11	0.01	0.62	0.19±0.14	0.006
Alpha Amino Butyric Acid	5.85	20.07	11.29±4.43	2.21	25.04	13.32±6.12	0.261
Beta Amino İsobutyric Acid	0.04	10.90	3.68±3.28	1.00	4.05	2.66±0.90	0.116
Gamma Amino Butyric Acid	20.13	63.21	40.05±14.06	0.32	7.72	4.89±1.70	<0.001
Beta Alanine	2.03	8.61	4.81±2.08	0.15	6.34	3.04±1.05	0.005
Cystathionine	0.01	0.19	0.09±0.06	0.01	0.50	0.12±0.12	0.981
Thiaproline	0.02	0.47	0.15±0.14	0.00	0.23	0.08±0.06	0.135
1-Methylhistidine	0.63	3.45	1.86±0.85	0.62	1.92	1.30±0.37	0.026
3-Methylhistidine	0.12	4.10	1.22±1.06	0.09	4.85	0.66±1.15	0.002
Hydroxylysine	0.03	0.42	0.16±0.13	0.01	0.60	0.15±0.14	0.463
Hydroxyproline	37.54	142.68	79.21±32.05	1.16	41.45	25.67±10.39	<0.001
Homocystin	1.25	1.90	1.18±0.43	0.41	0.74	0.17±0.18	<0.001
Serotonin	0.01	1.99	0.48±0.57	0.00	1.09	0.10±0.25	<0.001
Histamine	0.01	0.03	0.02±0.01	0.00	0.08	0.02±0.02	0.019
Ethanolamine	1.15	18.19	10.96±5.02	1.16	35.41	7.26±6.21	0.007
Phosphoethanol Amine	20.47	122.39	67.66±34.67	0.00	85.20	28.38±24.45	0.001
5-OH Tryptophan	0.05	0.57	0.23±0.15	0.00	0.50	0.04±0.09	<0.001
Taurine	208.37	1514.27	688.51±394.13	11.93	161.03	78.29±37.28	<0.001

DISCUSSION

Patients with FMS have significantly reduced levels of serum amino acids compared to healthy controls, which concurs with the existing literature.

Small molecules, such as peptides, oligonucleotides, sugars, nucleosides, organic acids, ketones, aldehydes, amines, amino acids, lipids, steroids, alkaloids, drugs, and human bacterial products, with molecular weights below 1, 500 Da, are considered metabolites (10). Metabolomics uses high-throughput technologies for the detection, quantification, and identification of these small molecule metabolites arising from lipids, carbohydrates, vitamins, hormones, and other cell components in tissues and physiological fluids over a certain period of time. It is well known that abnormalities in amino acid uptake and metabolism occur in many diseases, highlighting the role of specific amino acids in disease pathology. At the cellular level, aerobic physical activity increases the amount and quality of muscle mitochondria, which results in increased muscle oxidation capacity and exercise tolerance (11). As amino acids play an important role in genotoxicity, oxidative stress, and nutritional stress, abnormalities in amino acid levels presumably affect the physiology of patients with FMS (12).

Previous studies have reported that long-term and vigorous physical activities are associated with low blood levels of valine, leucine, and isoleucine, and blood glucose metabolism; accordingly, it is proposed as an

indicator of fatty acid oxidation in lipid metabolism. Furthermore, blood levels of glutamate and 2-hydroxybutyrate amino acids are inversely related to physical activity. These amino acids are involved in critical mechanisms in energy regulation and protein synthesis, such as the metabolism of glutamate and cysteine, and in the tricarboxylic acid (TCA) cycle (13-16).

Decreased values of some amino acids have been reported in patients with pancreatic, thyroid, or gastrointestinal diseases, and FMS (17, 18). In our study, the patient group had significantly reduced levels of the following free amino acids–alanine, arginine, aspartic acid, citrulline, glutamine, glutamic acid, glycine, histidine, leucine, isoleucine, alloisoleucine, lysine, phenylalanine, proline, serine, tryptophan, tyrosine, hydroxyproline, cystine, homocysteine, serotonin, and taurine.

In living organisms, many cellular proteins are constantly degraded and resynthesised to ensure that they are available as sources of energy and amino acids in the case of nutritional deficiency. Presumably, the pathophysiology of FMS causes a decrease in the body's amino acid pool. Amino acids are key elements in the maintenance of a constant cycle of protein synthesis and degradation and are essential to sustaining the body's protein balance (20, 21). In our study group comprising patients with FMS, there were significant changes in the amino acid profiles of phenylalanine and citrulline, and for 3-MMH only in the amino acid phenylalanine, compared to the control group. Additionally, the patient group showed significant lower in glycine, and glutamate amino acids compared to the control group.

BCAAs (valine, leucine and isoleucine) are alternative sources of organic molecules that can also fuel the TCA cycle (20, 21). We observed a statistically significant difference in the levels of BCAAs in patients with FMS compared to the healthy control group; however, no such difference was observed between the groups regarding the amino acid's asparagine, ornithine, methionine, and threonine. Like bioenergetic pathways, biosynthetic pathways are also based on various amino acid contributions (22, 23). The catabolism of BCAAs can mediate lipogenesis through acetyl-CoA synthesis. Likewise, nucleotide synthesis, which can be divided into purine and pyrimidine biosynthesis, is another amino acid-dependent process in which glycine, glutamine, and aspartate serve as carbon and nitrogen donors for purine biosynthesis.

Essential and nonessential amino acids are important for the development of all cells and the biosynthesis of lipids and nucleotides (24). Aa's are especially involved in reducing the effect of oxidative stress, producing glutathione, and adjusting the balance of oxidation and reduction. Furthermore, the formation of nonessential amino acids occurs through the catabolism, transamination, and chemical reactions of essential amino acids (25, 26). In the central nervous system, serotonin (5-hydroxytryptamine, 5-HT) is synthesised from tryptophan, an essential amino acid. Presynaptic autoreceptors on serotonergic neurons control the release of 5-HT in terminal areas, which inhibits serotonergic signalling (27). The low tryptophan in our study supports the disorder in the functional activity of brain structures in patients with FMS.

Recent research has shown that amino acids play an important role in immunity against viral, bacterial, and fungal infections (28, 29). Additionally, amino acids regulate immune activation and suppress inflammation resulting from infection. Therefore, amino acids, especially tryptophan, play a crucial role in protecting host tissues against infections by reducing excessive inflammatory reactions (30). It is well known that FMS may be triggered secondarily to the body's inflammatory response to infection. The low rate in our study supports this.

The most important limitation of our study is that only female patients were included, the disease is more common in women, thus ensuring homogeneity between groups and eliminating gender-related variables. There is a need for studies with larger participation including men.

CONCLUSION

We obtained data supporting central nervous system changes and inflammatory pathogenesis in the etiopathogenesis of FMS.

Patients with FMS have significantly reduced levels of serum amino acids compared to healthy controls. The pathophysiology of FMS remains unclear; consequently, no definitive treatment is available. We believe that our findings will contribute to the development of diagnostic and therapeutic strategies for FMS; nevertheless, further research is warranted on this subject..

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval for the study was obtained from the Harran University Clinical Research Ethics Committee (approval number: 23/10/04; dated: 05.06.2023).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Montserrat-de la Paz S, Garcia-Gimenez MD, Angel-Martin M, Fernandez-Arche A. Validation and additional supportfor an experimental animal model of fibromyalgia. Mod Rheumatol. 2015;25:116–22.
2. Dumas ME, Davidovic L. Metabolic Profiling and Phenotyping of Central Nervous System Diseases: MetabolitesBring Insights into Brain Dysfunctions. J Neuroimmune Pharmacol. 2015;10:402–24.
3. DeSantana JM, da Cruz KM, Sluka KA. Animal models of fibromyalgia. Arthritis Res Ther. 2013;15:222.
4. Tatum WO, Langston ME, Acton EK. Fibromyalgia and seizures. Epileptic Disord. 2016;18:148–54.
5. Srinivas SR, Prasad PD, Umapathy NS, Ganapathy V, Shekhawat PS. Transport of butyryl-L-carnitine, a potentialprodrug, via the carnitine transporter OCTN2 and the amino acid transporter ATB(0,+) Am J Physiol Gastrointest Liver Physiol. 2007;293:1046–53.
6. Manner T, Katz DP, Askanazi J. The antinociceptive effects of branched-chain amino acids: evidence for their ability to potentiate morphine analgesia. Pharmacol Biochem Behav. 1996;53:449–54.
7. Gordon M. Comment on Biogenic amine depletion as a putative animal model of fibromyalgia, Pain. 2010;148(1):172–3.
8. Blachier F, Blais A, Elango R, Saito K, Shimomura Y, Kadowaki M. Tolerable amounts of amino acids for human supplementation: summary and lessons from published peer-reviewed studies. AminoAcids 2021;53:1313–28.
9. Wolfe F, Clauw DJ, Fitzchar!es MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010;62:600-1.
10. Marino C, Grimaldi M, Sabatini P, et al. Fibromyalgia and Depression in Women: An 1H-NMR Metabolomic Study. Amino acid profling as a method of discovering biomarkers for diagnosis of neurodegenerative diseases. Metabolites 2021;11:429.
11. Hofman JM, Lyu Y, Pletcher SD, Promislow DE. Proteomics and metabolomics in ageing research: from biomarkers to systems biology. Essays Biochem 2017;61(3):379–88.
12. Wood K, Harwood J, Swade C, Coppen A. Decreased tryptophan excretion by depressive patients. Clin Chim Acta. 1978;88:57–61.
13. Curzon G, Bridges PK. Tryptophan metabolism in depression. J Neurol Neurosurg Psychiatry. 1970;33:698–704.
14. Beth Kelly, and Erika L. Pearce. Amino Assets: How Amino Acids Support Immunity. Cell Metabolism 2020;32:155-8.
15. Wood K, Harwood J, Swade C, Coppen A. Decreased tryptophan excretion by depressive patients. Clin Chim Acta.1978;88:57–61.
16. Lieu EL, Nguyen T, Rhyne S, Kim J. Amino acids in cancer. Exp Mol Med. 2020;52(1):15-30.
17. Piras C, Arisci N, Poddighe S, Liggi S, Mariotti S, Atzori L. Metabolomic profile in hyperthyroid patients before andafter antithyroid drug treatment: correlation with thyroid hormone and TSH concentration. Int. J. Biochem. Cell Biol.2017;93:119–28.
18. Raouf AA, El-Sebaey HM, Abd El-Hamead AK, El-Fert AY, El-Gendy YE. Plasma free amino acid profle changes in hepatocellular carcinoma patients. Menoufa Med J 2016;29:895–90.
19. Assche R, Temmerman L, Dias DA, et al. Metabolic profling of a transgenic Caenorhabditis elegans Alzheimer model. Metabolomics. 2015;11(2):477–86.
20. Figura M, Kuśmierska K, Bucior E, et al. Serum amino acid profle in patients with Parkinson's disease. Plos One 2018;13(1):1–12.
21. Malatji BG, Mason S, Mienie LJ, et al. The GC-MS metabolomics signature in patients with fibromyalgia syndrome directs to dysbiosis as an aspect contributing factor of FMS pathophysiology. Metabolomics. 2019;15(4):54.
22. Menzies V, Starkweather A, Yao Y, et al. Metabolomic Differentials in Women With and Without Fibromyalgia. Clin Transl Sci. 2020;13(1):67-77.
23. Gupta S, Sharma U. Metabolomics of neurological disorders in India. Analytical Science Advances. 2021:594-605
24. Welsch P, Bernardy K, Derry S, Moore RA, Häuser W. Mirtazapine for fibromyalgia in adults. Cochrane Database Syst Rev. 2018;8(8):CD012708.
25. Pagliai G, Giangrandi I, Dinu M, Sofi F, Colombini B. Nutritional interventions in the management of fibromyalgia syndrome. Nutrients 2020;12:2525.
26. Piras C, Conte S, Pibiri M, et al. Metabolomics and psychological features in fibromyalgia and electromagnetic sensitivity. Scientific Reports. 2020;10:20418
27. Rezende RM, Gouveia Pelúzio MDC, de Jesus Silva F, et al. Does aerobic exercise associated with tryptophan supplementation attenuates hyperalgesia and inflammation in female rats with experimental fibromyalgia?. PLoS One. 2019;14(2):e0211824.
28. Bröer S, Gauthier-Coles G. Amino Acid Homeostasis in Mammalian Cells with a Focus on Amino Acid Transport. J Nutr Biochem 2017;474:1935–63.
29. Menzies V, Starkweather A, Yao Y, et al. Metabolomic differentials in women with and without fibromyalgia. Clin Transl Sci. 2020;13(1):67-77.
30. Gibson EL, Vargas K, Hogn E, et al. Effects of acute treatment with a tryptophan-richprotein hydrolysate on plasma amino acids, mood and emotional functioning in older women. Psychopharmacology.2014;231:4595–610.