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Associations of serum arginine acid with sarcopenia in Chinese eldely women

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Abstract

Background The prevalence of sarcopenia is increasing in worldwide with accelerated aging process. The high dietary protein intakes are associated with improved muscle mass and strength especially in Asian countries. However, there are few researches on amino acid levels or mechanism exploration. We conducted a case-control study to explore the amino acid metabolic characteristics and potential mechanism of elderly women with sarcopenia using targeted amino acid metabolomics approach combined with an analysis of dietary intake.

Methods For our case-control study, we recruited women (65–75 y) from a Shanghai community with 50 patients with sarcopenia and 50 healthy controls. The consensus updated by the Asian Working Group on Sarcopenia in 2019 was used to screening for sarcopenia and control groups. We collected fasting blood samples and evaluated dietary intake. We used the amino acid-targeted metabolomics by ultra performance liquid chromatography tandem mass spectrometry to identify metabolic differentials between the case and control groups and significantly enriched metabolic pathways.

Results The case (sarcopenia) group had a lower intake of energy, protein, and high-quality protein ($P<0.05$) compared to the control (healthy) group. We identified four differential amino acids: arginine ($P<0.001$) and cystine ($P=0.003$) were lower, and taurine ($P=0.001$) were higher in the case group.

Conclusion Low levels of arginine in elderly women are associated with a higher risk of sarcopenia.

Keywords Sarcopenia, Metabolomics, Elderly women, Arginine acid

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Introduction

With approximately 14.2% of its population over the age of 65, China is exceeding the international standard for an aging society (65+, 7%) and has one of the highest aging rates in the world [1]. The proportion of elderly people in Shanghai is 18.7%, which is 1.32 times higher than the Chinese average. One of the typical presentations of aging is a decline in skeletal muscle mass and function [2], which may evolve into sarcopenia. Sarcopenia, which increases the risk of falls and fractures in older adults, leads to loss of independence, reduces quality of life, contributes to long-term care costs, and increases mortality risk [3, 4]. In China, the prevalence of

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sarcopenia (17.4%) is higher than in many countries such as Japan (9.9%) and Brazil (17.0%) [5]; in Shanghai, the prevalence of sarcopenia is 19.37% [6].

As a natural degenerative disease, sarcopenia can be prevented. Studies have shown that high dietary protein intakes (above the current recommended dietary allowance and up to 1.2 g/kg/d) are associated with improved muscle mass and strength [7, 8] especially in Asian countries [9, 10]. Dietary protein plays roles in the metabolism and function of skeletal muscle [11]. Scientists have identified the advantages of amino acids in improving muscle function and preventing sarcopenia through nutritional intervention methods, both in human [12] and animal [13] studies.

Amino acids have different physiological roles. Previous studies on sarcopenia have mostly focused on dietary protein supplementation; therefore, it has been challenging to identify the amino acids that impact sarcopenia. Scientists have reported that changes in amino acid levels increase the risk of sarcopenia in American and Japanese women[14, 15], suggesting that changes in plasma amino acid profiles might be conducive to the development of sarcopenia [16].

Amino acid targeted metabolomics is a powerful tool for measuring age-related metabolic signatures to quantify serum amino acid levels and provide early biomarkers. In recent years, metabolomics has been used to examine the effects of amino acids on sarcopenia. A study on Caucasian females reported that aspartate and glutamic acid were significantly associated with muscle mass and strength [17]. A study on 20 men from the Korean Frailty and Aging Cohort Study concluded that tryptophan may be associated with the development of sarcopenia [18]. However, opposite findings have been reported for leucine and methionine [19]. It is possible that ethnic diversity might contribute to these differences, making it difficult to extrapolate the results. Unfortunately, China has relatively little research in this area and there is an urgent need for local research to improve intervention methods.

We conducted a case-control study to explore the amino acid metabolic characteristics of elderly women with sarcopenia in Shanghai using ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS) targeted amino acid metabolomics approach combined with an analysis of dietary intake.

Methods

Participants

Our community-based case-control study recruited subjects from two community health centers in Shanghai (Ganquan Street Community Health Center, Putuo District, and Laoximen Community Health Center, Huangpu District), with a total of 50 patients with sarcopenia, and 50 healthy controls, matched by age (±1 year) and the same number of chronic diseases and the same disease that most affect health.

The study participants were women who were able to walk independently, had no cognitive impairment, and volunteered to participate in our study. Participants with infectious diseases, diseases affecting the liver or kidney, hypertensive patients whose blood pressure exceeds the standard after taking medicine, diabetic patients whose blood sugar exceeds the standard after taking medicine, those with long-term use of medications (e.g., hormone therapy drugs and weight loss medications) were excluded from the study.

Sarcopenia criteria

We assessed sarcopenia by measuring the subjects' pace test, dominant handgrip strength, and skeletal muscle index, and used the consensus updated by the Asian Working Group on Sarcopenia in 2019 [20] as the screening criteria for sarcopenia and control groups, which were consistent with a previous study by our project team [21].

Data and biological sample collection

We obtained information from all participants including dietary intake and disease history. Additionally, we performed a physical examination. We used a food frequency questionnaire to obtain information on the dietary intake, converted each food according to its requirement (raw weight, edible part weight, dry weight, fresh weight, etc.) based on the conversion ratio, and then calculated each nutrients by referencing the Chinese Food Composition Table. The intake frequency was never, times/day, times/week, times/month, times/quarter. The food groups included staple foods, coarse grains, mixed beans, potatoes, soybeans and their products, vegetables, pickled vegetables, mushrooms and algae, fruits, dairy, livestock, fish and shrimp, eggs, nuts, beverages, and dietary supplement with supplement-oriented nutrients.

High-quality protein was defined as protein from soybeans and their products, livestock, fish and shrimp, eggs, dairy products, preserved animal foods, and dietary supplements.

We collected 5 mL of fasting blood from the participants and centrifuged it at 1,400 relative centrifugal force (RCF) for 10 min over 4 h. We stored the supernatant in cryogenic vials, transported them to the laboratory within 4 h, and stored them at −80 °C for amino acid targeted metabolomics analysis.

Amino acid targeted metabolomics analysis

To each sample, we added 500 μL of 80% methanol, treat five times in an ice-water bath in a cycle of "ultrasound for 1 min and static for 1 min". We stored the sample at

−40 °C for 30 min and at 4 °C for 10 min. Following centrifugation at 15,000 RCF for 15 min at 4 °C, we dried the supernatant under a mild nitrogen stream. Following the addition of 50 μL sodium carbonate (100 mM) and 50 μL benzoyl chloride (2%), we mixed the sample for 30 s and centrifuged it for 15 min. We mixed equal volumes of supernatant and isotope internal standard solution; each of the sample was mixed in equal volumes (20 μL) to obtain quality control samples.

A working solution containing amino acids (10 μmol/L) were mixed from each standard stock solution and prepared as the same protocol of sample preparation. The solution was serially diluted to obtain a standard curve solution (0.01–10 μmol/L) and mixed with an equal volume of isotopic internal standard solution to obtain the final quantitative amino acid calibration standard curve (0.005–5 μmol/L).

We processed the raw data, using default parameters and manual checks to ensure the qualitative and quantitative accuracy of each compound. We performed regression analysis using the peak area ratio of each compound standard to the obtained internal standard. We generated a 10-point quantitative standard curve to quantify the levels of amino acids (C, nmol/L) in the prepared samples. The final concentration were calculated according to the dilution ratio when sample preparation.

For the chromatographic separation of the compounds, we used an Agilent 1290 infinity ultra performance liquid chromatography (Aglient, USA) coupled to a Zic-HILIC column (3.5 μm, 2.1 mm × 150 mm). We conducted mass spectrometry in positive ion mode using a Agilent 6545 Q-TOF tandem mass spectrometry (Aglient, USA). The source condition parameters were the following, ion source temperature of 500℃, ion source atomization gas (Gas 1) of 40, auxiliary heating gas (Gas 2) of 40, curtain gas of 30, and spray voltage of 5,500 V. We used the multiple reaction monitoring mode to detect ion pairs. The MultiQuant software was used to extract the peak area and retention time, and the retention time was corrected with standards of amino acids and their derivatives for the metabolite identification.

We determined 28 amino acids and their derivatives in serum using UPLC-MS.

Statistical methods

Descriptive statistics

We analyzed the data using SPSS 21.0. We used the t-test for data that had a normal distribution and expressed the data as mean ± standard deviation. We used the Mann–Whitney U-test for data that did not have a normal distribution and expressed the data as median (P25, P75). We used Chi-square test for rank data. $P<0.05$ was considered statistically significant. After screening for factors with differences that were statistically significant, logistic regression analysis was used to adjust for confounders.

Serum amino acid analysis

The degree of aggregation of quality control samples was examined using principal component analysis (PCA). PCA and orthogonal partial least squares discriminant analysis (OPLS-DA) were performed on the case (sarcopenia) and control (healthy) groups. The variable importance in the projection of the OPLS-DA model (VIP ≥ 1) was used and combined with the independent sample t-test ($P<0.05$) to identify differential metabolites. The differential metabolites of the two groups were mapped to KEGG ID by online software MetaboAnalyst 2.0 (https://github.com/xia-lab/MetaboAnalystR). Homo sapiens was chosen as the species for pathway analysis.

The OPLS-DA model used orthogonal signal correction technology to filter information unrelated to inter group classification and maximize the calculation of inter group differences. The model validation was based on the cross-validation method, and the number of cycles for the permutation test was 200, and the obtained R2Y and Q2 (representing the model explanatory variables and model predictability, respectively) were used to evaluate the model's classification effect.

Results

Basic information

Table 1 shows the basic characteristics of the participants. Education level, skeletal muscle mass, and body mass index (BMI) prevalence were lower in the case than in the control group ($P<0.05$). There was a significant difference in educational level between the two groups ($P<0.05$). Other characteristics did not differ significantly between the two groups.

Dietary intake

Table 2 shows that the case group had a lower intake of energy, protein, and high quality protein ($P<0.05$) and a higher intake of sodium ($P<0.05$). However, the differences between the two groups in terms of food intake were not statistically significant.

Metabolomics analysis

The quality control samples showed a high correlation ($r>0.99$), indicating little intra-group variation. Relative standard deviation (RSD) was <30% for each of the compounds, indicating that the experimental data were stable and reliable with good reproducibility. The OPLS-DA score plot showed a clear trend towards separation between the two groups, and the currently established discriminant model with R2Y cum = 0.366 ($P<0.05$) and Q2 cum = 0.129 ($P<0.05$) allowed for a valid distinction between the two samples, indicating that there were

Table 1 Basic information of study participants

	Case group (*n* = 50)	Control group (*n* = 50)	t/X^2	*P*
Age, y	68.44 ± 3.47	68.74 ± 3.36	-0.439	0.661
Education level, n (%)			7.349	0.026
High school and above	12 (24.0)	25 (50.0)		
Junior High School	32 (64.0)	22 (44.0)		
Primary School and below	6 (12.0)	3 (6.0)		
Occupation, n (%)			0.198	0.656
Physical work oriented	13 (26.0)	15 (30.0)		
Mainly mental work	37 (74.0)	35 (70.0)		
Marital status			0.638	0.424
Divorced or widowed	10 (19.2)	7 (14.0)		
Married	40 (76.9)	43 (86.0)		
Skeletal muscle mass, kg	13.49 ± 1.32	16.92 ± 1.78	-10.957	< 0.001
BMI, kg/m²	22.53 ± 2.33	24.08 ± 2.44	-3.238	0.002
Body fat percentage, %	35.26 ± 5.38	35.77 ± 5.62	-0.469	0.640
Waist-to-hip ratio	0.91 ± 0.06	0.92 ± 0.05	-0.877	0.383
physical activity (minute per day), medain (P25, P75)	0.00 (0.00, 5.36)	0.00 (0.00, 30.00)		0.138
Chronic disease status				
Stroke, n (%)	12 (24.0)	11 (22.0)	0.056	0.812
Coronary heart disease, n (%)	12 (24.0)	9 (18.0)	0.542	0.461
Hypertension, n (%)	21 (42.0)	28 (56.0)	1.961	0.161
Hyperlipidemia, n (%)	11 (22.0)	17 (34.0)	1.786	0.181
Diabetes, n (%)	14 (28.0)	12 (24.0)	0.208	0.648
Osteoporosis, n (%)	10 (20.0)	8 (16.0)	0.271	0.603

indeed metabolic differences between the case and control groups. The picture was shown in Fig. 1.

We performed a permutation test on the model, because the intercept of the regression line on the Y axis was <0, which can be considered to be reliable with no "over-fitting" (Fig. 2). Alternatively, receiver operating characteristic (ROC) curves and their corresponding area under the curve (AUC) were obtained (Fig. 3). Furthermore, the AUC between controls and sarcopenia group presented an outstanding discrimination of 88.56%. Overall, it demonstrated that these methods can efficiently discriminate clusters between classes. The ROC curve of 27 amino acids and their derivatives in serum calculated based on the oplsda sample scores were in supplementary Figure S1.

With respect to the differential metabolites, arginine (P=0.008) and cystine (P=0.024) were lower, and taurine (P=0.016) were higher in the case group compared to the control group by the multiple correction for the differential metabolites' identification (Table 3). Based on the differential metabolite heat map, the differential metabolites were different between samples.

Table 2 Daily dietary intake of study participants

	Case group (*n* = 50)	Control group (*n* = 50)	*P*
Energy and Nutrients			
Energy, KJ	6360.94 (5133.14, 7784.02)	8107.34 (6075.29, 10167.87)	0.005
Protein, g	67.54 (51.60, 84.75)	83.13 (64.80, 103.34)	0.010
High-quality protein, g	35.84 (25.88, 50.79)	45.73 (35.18, 63.70)	0.004
Fat, g	45.28 (31.73, 63.76)	53.24 (40.61, 75.74)	0.164
Carbohydrates, g	212.23 (182.84, 258.29)	215.00 (179.80, 316.40)	0.508
Calcium, mg	633.43 (445.67, 774.79)	711.19 (519.77, 1042.89)	0.063
Sodium, mg	17103.12 (15313.86, 20010.35)	15264.56 (13681.52, 15986.48)	< 0.001
Iron, mg	21.59 (18.37, 32.38)	22.69 (17.72, 30.21)	0.956
Vitamin A, μg RAE	289.38 (214.42, 406.42)	329.33 (233.85, 466.58)	0.331
Vitamin D, IU	0.08 (0.03, 0.23)	0.10 (0.06, 0.17)	0.481
Vitamin E, mg	14.78 (11.37, 23.63)	17.02 (12.16, 25.96)	0.424
Vitamin K, μg	48.05 (31.23, 72.08)	48.05 (30.06, 96.10)	0.564
Thiamin, mg	0.89 (0.72, 1.06)	0.89 (0.74, 1.20)	0.424
Riboflavin, mg	1.10 (0.87, 1.39)	1.16 (0.92, 1.71)	0.215
Vitamin C, mg	85.35 (58.40, 122.85)	84.12 (60.55, 122.32)	0.923
Different food types			
Staple foods, g	178.10 (150.00, 237.95)	179.85 (139.30, 233.30)	0.775
Soybeans and their products, g	8.60 (4.33, 20.48)	8.30 (4.60, 13.38)	0.600
Mushrooms and algae, g	30.25 (18.05, 35.65)	36.40 (10.53, 66.23)	0.593
Dairy, g	180.85 (109.70, 315.00)	240.00 (59.60, 359.38)	0.430
Livestock, g	43.05 (41.20, 103.83)	63.80 (24.15, 82.10)	0.051
Fish and shrimp, g	37.20 (27.10, 64.40)	41.70 (24.33, 95.90)	0.687
Eggs, g	55.00 (50.00, 61.08)	51.70 (27.35, 75.88)	0.928
Nuts, g	4.60 (2.70, 25.00)	12.15 (1.08, 15.03)	0.075

The partial correlation analysis of the differential amino acids by adjustment for confounders

The results of partial correlation analysis by adjustment the age, Education level, Body fat percentage and physical activity showed that, high arginine (r=-0.16, P=0.018) and cystine (r=-0.25, P=0.027) were the protective factor against sarcopenialower, and high Glutamic (r=0.26, P=0.010) acid and taurine (r=0.37, P<0.001) were the risk protective factor (Table 4).

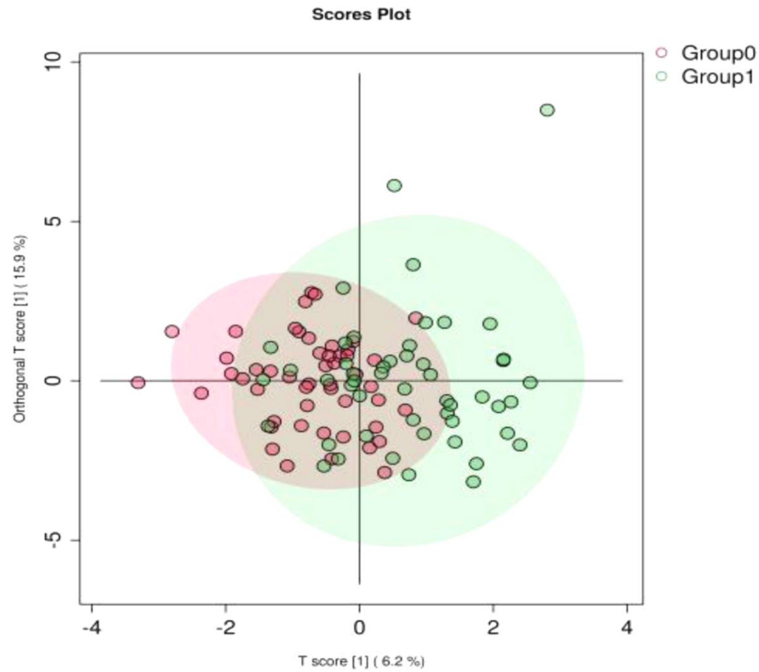

Fig. 1 OPLS-DA score plots for two groups. *Group 0 indicates control group and group 1 indicates case (sarcopenia) group

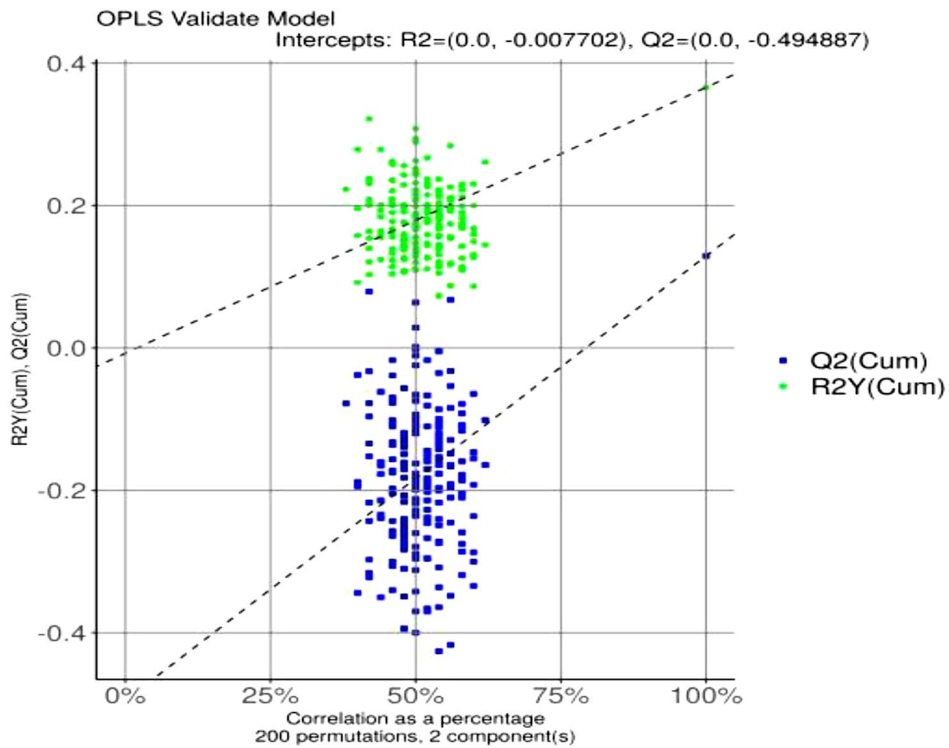

Fig. 2 Permutation test plot of the OPLS-DA model for two groups. *Group 0 indicates control group and group 1 indicates case (sarcopenia) group

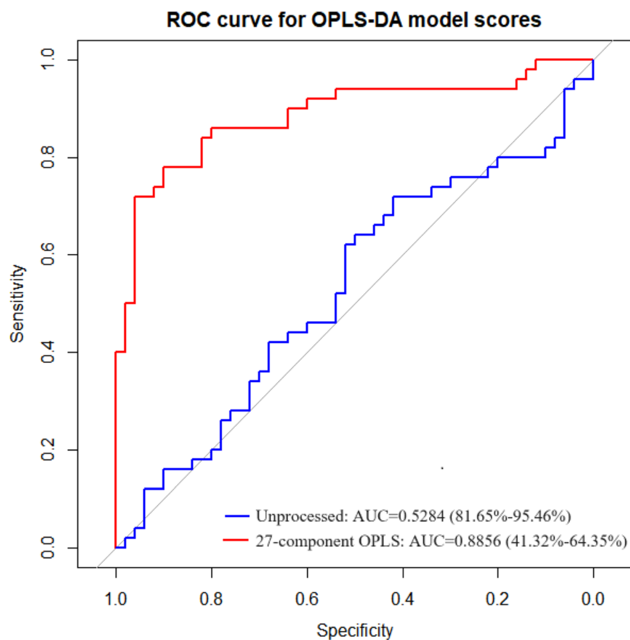

Fig. 3 Receiver operating characteristic (ROC) curves after the application of Orthogonal projection of latent structures (OPLS)- partial least squares discriminant analysis (PLS-DA)

Table 3 Serum differential metabolites

Amino acid	VIP	FC	Log_2(FC)	*P*	P_adjust
Arginine	2.89	0.89	-0.18	**< 0.001**	**0.008**
Cystine	1.88	0.87	-0.20	**0.003**	**0.024**
Glutamic acid	1.47	1.09	0.13	**0.025**	0.160
Taurine	2.44	1.28	0.35	**0.001**	**0.016**

Table 4 Serum differential metabolites

Metabolite	*r*	*P*
Arginine	-0.16	0.018
Cystine	-0.25	0.027
Glutamic acid	0.26	0.010
Taurine	0.37	**< 0.001**

Table 5 Key metabolic pathways

Pathway	Amino acid	*P*
Arginine biosynthesis	Arginine, glutamic acid	< 0.001
Arginine and proline metabolism	Arginine, glutamic acid	0.003
Aminoacyl-tRNA biosynthesis	Arginine, glutamic acid	0.005
Nitrogen metabolism	Glutamic acid	0.015
Alanine, aspartate, and glutamate metabolism	Glutamic acid	0.015
Taurine and hypotaurine metabolism	Taurine, glutamic acid	0.021
Butanoate metabolism	Glutamic acid	0.038
Histidine metabolism	Glutamic acid	0.041

Pathway analysis of differential metabolites

We obtained eight significantly enriched metabolic pathways ($P<0.05$): (1) arginine biosynthesis, (2) arginine and proline metabolism, (3) aminoacyl-tRNA biosynthesis, (4) nitrogen metabolism, (5) alanine, aspartate, and glutamate metabolism, (6) taurine and hypotaurine metabolism, (7) butanoate metabolism, and (8) histidine metabolism (Table 5; Fig. 4).

Discussions

Sarcopenia is a complex progressive disease, which is associated with an imbalance between protein synthesis and degradation [22] and a decline in metabolism after 40 y of age. The prevalence of sarcopenia increases significantly after 65 y of age [23, 24]. Exercise and dietary interventions are key factors in sarcopenia prevention, and the difference in moderate physical activity among the subjects in our study was not statistically significant, so it can be assumed that the disturbance of the exercise factor was excluded. When skeletal muscle mass increases, the risk of developing sarcopenia decreases. Serum amino acids affect muscle protein synthesis and sarcopenia development; hence, there has been an increasing interest in amino acids in recent years.

Our study identified four amino acids that were significantly different between the case (sarcopenia) and control (healthy) groups. Specifically, arginine and cystine were lower and taurine was higher in the case group. Additionally, we identified eight metabolic pathways that were significantly enriched: (1) arginine biosynthesis, (2) arginine and proline metabolism, (3) aminoacyl-tRNA biosynthesis, (4) nitrogen metabolism, (5) alanine, aspartate, and glutamate metabolism, (6) taurine and hypotaurine metabolism, (7) butanoate metabolism, and (8) histidine metabolism. Consequently, amino acid-based differential metabolites may Associations with sarcopenia.

In our study, arginine was the main differential amino acid, suggesting that older women with sarcopenia may be more susceptible to arginine levels. The aminoacyl-tRNA biosynthesis affects protein translation and is associated with the mammalian target of rapamycin complex 1 (mTORC1) [25]. The mTORC1 activity increases in old skeletal muscle causes damage to muscle fibers and may leads to sarcopenia, therefore, we should rather focus on mTORC1 inhibition [26–28]. Although Both arginine and leucine are the most potent mTORC1 activators [29, 30], they can also play an inhibitory role in some pathways [31]. Changes in amino acid levels due to dietary intakes are closely related to the activation of mTORC1 [32]. Our study found that the intake of arginine-rich livestock, fish, and shrimp was lower in the case than in the control group. The people in the case group had lower education and possibly lower income, which had possibly lower income and led to insufficient intake of expensive animal foods rich in arginine. A metabolomic study in two- and 21-month-old mice found that maintaining normal arginine levels in aged skeletal muscle is beneficial for combating sarcopenia [33]. In mammals,

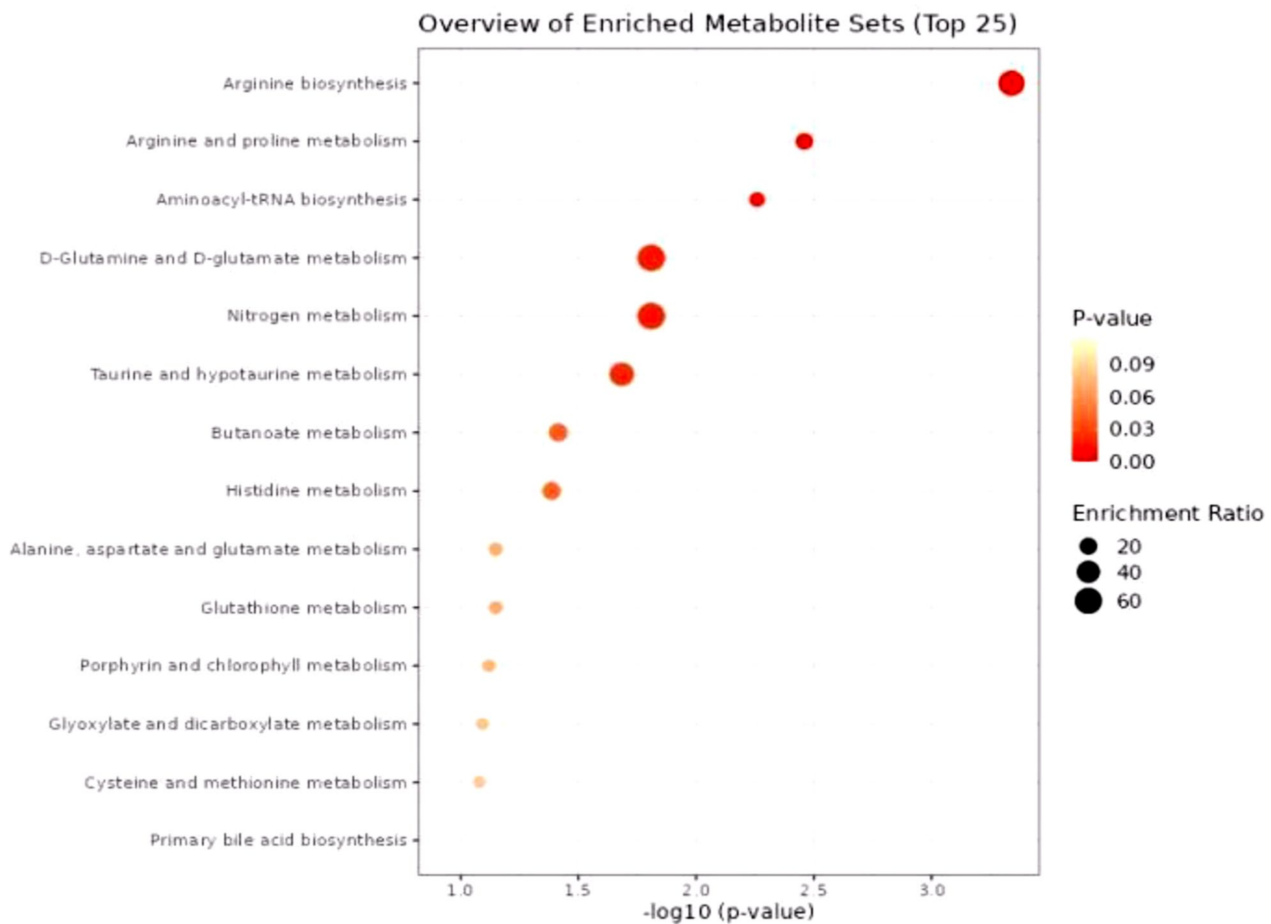

Fig. 4 Differential metabolite pathway enrichment analysis scatter-plot

arginine metabolism is complex and may prevent muscle fiber loss by minimizing oxidative stress through the NO, GSH synthesis, and Nrf2 signaling pathways [34].

Cystine, which is not involved in protein synthesis, has antioxidant properties. Oxidative stress is an important cause of aging and activates apoptotic signaling, leading to increased muscle loss [35]. Mitochondria control apoptosis. The mitochondrial cystine/glutamic acid reverse transporter is beneficial for cancer drug targeting [36]. A six-month controlled experiment in middle-aged mice concluded that dietary supplementation with cystine-based antioxidants effectively inhibited skeletal muscle apoptosis, thereby preventing age-related loss of skeletal muscle mass [37]. In our study, patients with sarcopenia had a lower intake of cystine-rich mushrooms, algae, and nutty foods compared to the healthy controls. Even though metabolomic studies have found insignificant differences in cystine levels, the link between the amino acid and sarcopenia has gradually become clearer.

In mammals, taurine is synthesized from the oxidation of intermediate products of methionine and cysteine metabolism after decarboxylation and is closely related to the metabolism of cystine and cysteine. Increased protein hydrolysis with age is accompanied by changes in skeletal muscle, along with a significant decrease in taurine level [38]. Taurine has a predictive value in sarcopenia development or reduced skeletal muscle loss [22, 39]. We obtained a significant up-regulation in taurine, consistent with the results obtained in weak and aging patients with sarcopenia [40]. The metabolic mechanisms of taurine are controversial as they are often observed in age-related diseases, such as osteoporosis and weakness. Taurine may be released from cells under oxidative stress or chronic inflammation [41]; whether this could explain the association between high taurine serum levels and sarcopenia remains to be explored.

Women who were underweight, less educated, and with inadequate energy and high-quality protein intakes were more likely to develop sarcopenia. This finding agreed with the results obtained in British women [23]. The intake of the same food groups varied considerably within the case group, while it was relatively stable within the control group and close to dietary guideline recommendations, suggesting that maintaining a healthy

dietary pattern is beneficial in the prevention and treatment of sarcopenia. However, as the differences are not statistically significant, a discussion of the metabolomic findings would be more useful than analyzing dietary intake.

Our study findings may be useful for the implementation of sarcopenia prevention strategies in aging cities. However, our study only examined elderly women volunteers from two community health centers, and there may be a selection bias; therefore, our findings cannot be applied to all sarcopenia patients in China. Subsequent studies should focus on men.

Conclusions

Our study found that serum amino acid in elderly women with sarcopenia was characterized by a lower of arginine and cystine and an higher of taurine. Individuals with or at risk of sarcopenia should consume foods rich in arginine and cystine, such as and high-quality protein.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00839-3.

Supplementary Material 1

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Author contributions
Zhengyuan Wang and Jiajie Zang designed research and managed the project; Zhengyuan Wang, Chao Hua and Yuhua chen analyzed data; Chao Hua and Yuhua chen wrote the paper; Zehuan Shi, Mengying Qu, Qi Song, Liping Shen, Wei Lu and Zhuo Sun conducted research. All authors have read and agreed to the final version of the manuscript.

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Data availability
Please contact author for data requests.

Declarations

Ethics approval and consent to participate
The study protocol was registered in the Chinese Clinical Trial Registry (ChiCTR2100048874). The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Shanghai Municipal Center for Disease Control and Prevention Ethical Review Committee (2019-46). Written informed consent has been obtained from the patients to publish this paper.

Competing interests
The authors declare no competing interests.

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