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ORIGINAL ARTICLE

The relationship between dietary branched-chain and aromatic amino acids with the regulation of leptin and FTO genes in adipose tissue of patients undergoing abdominal surgery

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Abstract

Recent studies have suggested that the interaction between diet and an individual's genetic predisposition can determine the likelihood of obesity and various metabolic disorders. The current study aimed to examine the association of dietary branched-chain amino acids(BCAAs) and aromatic amino acids(AAAs) with the expression of the leptin and FTO genes in the visceral and subcutaneous adipose tissues of individuals undergoing surgery. This cross-sectional study was conducted on 136 Iranian adults, both men and women, aged ≥18 years. The samples were selected from patients admitted for abdominal surgeries. The dietary intake of BCAAs and AAAs was determined using a valid and reliable 168-item food frequency questionnaire. Using the quantitative PCR method, leptin and FTO mRNA expression was measured in both visceral and subcutaneous fat tissues. The mean age of the participants was 39.8 ± 12.7 years, and the mean intake of BCAAs and AAAs was 17.7 ± 0.9 and 9.3 ± 0.3% of protein per day, respectively. In overweight-obese patients(body mass index = 25–34.9 kg/m^2), the intake of BCAAs(β:-0.75,95%CI:-1.47,-0.03), valine(β:-0.78,95%CI:-1.51,-0.05), and tyrosine(β:-0.81,95%CI:-1.55,-0.06) was inversely associated with FTO gene expression in subcutaneous fat tissue in adjusted model. In morbidly obese patients(body mass index ≥ 35 kg/m^2), a higher intake of total BCAAs(β:1.10,95%CI:0.07–2.13), leucine(β:1.07,95%CI:0.03–2.13), and isoleucine(β:1.49,95%CI:0.46–2.52) was associated with an increase of leptin gene expression in subcutaneous fat tissue. Our findings suggest that dietary BCAA may associated with gene expression in adipose tissues, potentially influencing obesity-related metabolic pathways. Further prospective studies are warranted to validate results and elucidate the potential for dietary interventions targeting amino acids intake in obesity management.

Keywords Adipose tissues · Leptin · FTO · Nutrigenomics · Obesity · Branched amino acids · Aromatic amino acids

Abbreviations

AAAs	aromatic amino acids
BCAAs	branched amino acids
BMI	Body mass index
FFQ	food frequency questionnaire
NIMAD	National Institute for Medical Research Development
MAQ	Modifiable Activity Questionnaire
FCT	Food Composition Tables
HDL-C	high-density lipoprotein-cholesterol
T2D	type 2 diabetes
TC	total cholesterol
LDL-C	low-density lipoprotein-cholesterol
PBS	phosphate-buffered saline
cDNA	complementary DNA
NCBI	National Center for Biotechnology Information
qPCR	quantitative PCR
NTC	non-template control
PKC	Protein kinase C

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PI3K phosphatidylinositol 3-kinases
ERK Extracellular signal-regulated kinases

Introduction

Obesity is a highly prevalent metabolic disorder and a major global health issue, directly associated with an increased risk of chronic diseases, such as type 2 diabetes (T2D), hypertension, and cardiovascular diseases (Blüher 2019). In addition to its related chronic conditions, obesity reduces quality of life and increases mortality (Abdelaal et al. 2017). Genetics, environmental factors, and their interactions are fundamental determinants of an individual's weight and risk of obesity (Heianza and Qi 2017; Qi and Cho 2008). Dietary patterns, as a crucial aspect of lifestyle, play a key role in predicting obesity. The interaction between diet and the genetic predisposition of individuals can influence the likelihood of obesity and various metabolic disorders (Swinburn et al. 2004; Heianza and Qi 2017).

Recently, research has investigated the relationship between amino acid intake and the risk of chronic diseases, including metabolic disorders (Mirmiran et al. 2019; Teymoori et al. 2018; Zhao et al. 2020; Okekunle et al. 2019). Findings indicate that certain amino acids, such as branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs), can have metabolic effects on adipose tissue (Orozco-Ruiz et al. 2022). Additionally, studies have identified genes such as leptin and FTO as common genetic predictors of obesity and metabolic disorders (Ali et al. 2021; Lan et al. 2020; Huong et al. 2021; Obradovic et al. 2021).

Recent studies have focused on the relationship between nutritional factors and the expression levels of the FTO and leptin genes in adipose tissue, yielding some interesting results (Yuzbashian et al. 2019, 2021; Rostami et al. 2017). One cross-sectional study revealed that higher intakes of total carbohydrates, sucrose, glucose, and lactose were inversely related to FTO gene expression in the subcutaneous adipose tissue, while dietary fructose was positively associated with FTO gene expression (Yuzbashian et al. 2019). Another investigation reported weak associations between dietary total fat, monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA) with FTO gene expression in both visceral and subcutaneous adipose tissues (Yuzbashian et al. 2021). Furthermore, habitual consumption of saturated fatty acids (SFAs), MUFA, and polyunsaturated n-3 fatty acids was related to leptin gene expression in visceral and subcutaneous adipose tissues (Rostami et al. 2017). The results of the above-mentioned studies suggest that both the quality and quantity of dietary intake, as well as nutrient composition, play important roles in FTO and leptin gene expression. However, to date, no studies have investigated the association between dietary intakes of BCAAs and AAAs and FTO and leptin gene expression in visceral and subcutaneous adipose tissues. Given that studies have shown some dietary compounds may affect gene expression in visceral and subcutaneous fat tissue, investigating the effect of branched-chain and aromatic amino acids intake on leptin and FTO gene expression in these tissues can provide valuable insights. This research could identify possible interactions between important nutritional factors and gene expression that influence adipose tissue.

Materials and methods

Study population

This cross-sectional study was conducted on 136 adult participants in Tehran, encompassing two groups, including overweight-obese patients (body mass index = 25 to 34.9 kg/m^2) and morbidly obese patients (body mass index ≥ 35 kg/m^2), aged ≥ 18 years. The sample size was calculated using a standard formula, and participants were selected from patients admitted for abdominal surgeries at Seyed Mostafa Khomeini and Khatam Al Anbia Hospitals in Tehran, Iran. Inclusion criteria required participants to have been hospitalized for at least three days and excluded those with T2D or cancer. Additional criteria included not using anti-lipid or weight-reducing medications, not being pregnant or breastfeeding, and not following a special diet.

Cohen's formula (Cohen 2013) was used to estimate the sample size for the current study, considering the average effect of macronutrient quality indices on the expression of leptin, FTO, and Omentin genes ($R^2 = 0.13$), with a two-sided significance level set at 5% ($\alpha = 0.05$) and power 80% (β:20%) for 5 variables (each variable of amino acid and four possible confounding variables, including age, gender, physical activity, and energy intake), the minimum sample size required for the present study was estimated to be 96 individuals. Considering the 30% possible losses of the included samples due to insufficient data and measurement errors in gene expression and other variables (30% of the estimated sample size), 130 individuals were determined as the final sample size of the current study.

$$\mathrm{N} = \frac{\lambda\left(1-R^2_{Y\cdot B}\right)}{R^2_{Y\cdot B}} + \mathrm{u} + 1$$

For this study, 50–100 mg samples of subcutaneous and visceral adipose tissues were collected from patients during different abdominal surgeries which included general abdominal surgeries such as hernia repairs (inguinal, umbilical, and hiatal hernias), operations related to appendix and

gallbladder disorders, bariatric surgery, as well as surgeries involving the bladder, kidneys, ovaries, and prostate. Exclusion criteria for the current study included responding to less than 70% of the food items on the food frequency questionnaire (FFQ), underreporting or over-reporting calorie intake (less than 800 kcal or more than 5000 kcal per day), withdrawal from the study for any reason, incomplete gene expression data due to issues such as storage and analysis errors of the fat tissue samples, and discovering that the participant had diabetes after determining their fasting blood glucose level.

The written informed consent form was obtained from volunteer patients before their inclusion in the study, and a fasting blood sample was collected from each participant before surgery. All participant information was kept confidential by the research team. All procedures involving human participants adhered to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was assessed and approved by the ethics research committee of the National Institute for Medical Research Development (NIMAD), Tehran, Iran.

Measurements

Data on demographic variables, socioeconomic status, disease history, and medications were collected. Body weight was measured to the nearest 100 g using a digital scale, with participants wearing minimal clothing and no shoes. Height was measured to the nearest 0.5 cm using a stadiometer, with participants standing without shoes and with their shoulders in a normal position. Body mass index (BMI) was defined as an individual's weight in kilograms divided by the square of their height in meters. Physical activity data were determined using the Modifiable Activity Questionnaire (MAQ), which has been updated and validated for use among Iranians (Momenan et al. 2012).

Data on dietary intakes were collected using a valid and reliable semi-quantitative 168-item food frequency questionnaire (Esfahani et al. 2010; Mirmiran et al. 2010). A trained nutritionist asked participants to indicate their consumption frequency for each food item over the previous year, daily, weekly, or monthly. Portion sizes of consumed foods, reported in household measures, were then converted to grams. Amino acid intake was determined using the USDA Food Composition Tables (FCT), which are based on the chemical analysis of amino acid composition. Values for BCAAs (leucine, isoleucine, and valine) and AAAs (phenylalanine, tryptophan, and tyrosine) were assigned to each FFQ food item. BCAAs and aromatic intake were then calculated by multiplying the frequency of consumption of each food item by its content of leucine, isoleucine, valine, phenylalanine, tryptophan, and tyrosine (Asghari et al. 2018).

Leptin and FTO mRNA levels in adipose tissues were measured using real-time quantitative PCR (qPCR). Total RNA was extracted from subcutaneous and visceral fat tissues following the manufacturer's protocol. Tissue samples (30–50 mg) were cut and added to 1 mL of TRIzol reagent (Invitrogen, U.S.). The mixture was homogenized, and chloroform was added to separate the phases. Proteins, lipids, carbohydrates, and cell debris were removed by extracting the aqueous phase. The quality of the extracted RNA was assessed using a Nanodrop spectrophotometer (ND-1000, Thermo Scientific, USA) by measuring the 260/280 and 260/230 nm absorption ratios. Total RNA was treated with DNase I to eliminate any residual genomic DNA before synthesizing complementary DNA (cDNA). The cDNA synthesis kit (BIOFACT, South Korea) was used according to the manufacturer's instructions, and the resulting product was stored at -20 °C for further analysis.

Primers were designed based on sequences from the National Center for Biotechnology Information (NCBI) and were checked using Genrunner Software (version 3.05). The GAPDH gene was used as the reference gene for normalization across samples. For each gene, including FTO and leptin, a pair of forward and reverse primers were generated.

Real-time quantitative PCR (qPCR) was conducted using a Rotor-Gene 6000 instrument (Sydney, Australia) in 25µL volumes comprising 12.5µL of 2X SYBR Green Master mix (BioFact, Korea), 0.3µL of forward primers, 0.3µL of reverse primers, 8.9µL of RNase and DNase -free water, and 3µL of cDNA. Each gene was analyzed in duplicate to ensure inter-assay control, alongside GAPDH as a housekeeping gene and non-template control (NTC). The qPCR amplification followed these thermal cycling conditions: initial denaturation at 95 °C for 5 min, followed by 45 cycles at 95 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s for annealing, amplification, and quantification, respectively. The relative expression of each gene in the samples was calculated based on its threshold cycle (Ct) value, normalized to the Ct of the reference gene. All qPCR procedures adhered to MIQE guidelines (Bustin et al. 2009).

Statistical analysis

All analyses were performed using the Statistical Package for Social Sciences (Version 20.0; SPSS, Chicago, IL). The Kolmogorov-Smirnov test was used to assess the normality of the variables. Baseline characteristics of the participants were presented as the mean ± SD or median (25–75 interquartile range) for continuous variables and as percentages for categorical variables in two groups, including

overweight-obese patients and morbidly obese patients. Participants were categorized according to quartiles of BCAAs and AAAs. The Chi-square test and linear regression analyses were utilized to examine trends in categorical and continuous variables across the quartiles of BCAAs and AAAs, respectively. Linear regression was also used to determine the relationship between BCAAs and AAAs intake and leptin and FTO mRNA levels in visceral and subcutaneous fat tissues. Standardized β values were reported, adjusted for age, sex, and physical activity.

Results

In the present study, the mean BMI and age of the participants were 39.4±8.5 kg/m^2 and 39.8±12.7 years, respectively. The mean BCAAs and AAAs intake among participants was 17.7±0.9 and 9.3±0.3% of protein/day. Table 1 shows the demographic characteristics and dietary intake of the participants based on their obesity status. Our finding showed that patients with overweight-obesity had significantly higher mean age ($P<0.001$) and physical activity ($P=0.043$) levels compared to those with morbid obesity. Overweight-obese patients also had a higher percentage of carbohydrates in their total energy intake compared to morbidly obese patients ($P<0.005$). In contrast, total energy intake, and fat percentage of total energy intake were significantly higher in morbidly obese patients ($P<0.005$). No significant differences were found between the groups for other demographic characteristics and dietary intake.

Table 2 presents the relationship between the intake of BCAAs and AAAs as a percentage of total protein intake, along with their components, and the expression of FTO and leptin genes in subcutaneous and visceral fat among overweight-obese patients undergoing bariatric surgery. In the adjusted model, total BCAAs (β:-0.75, 95%CI:-1.47, -0.03, $P=0.041$), valine (β: -0.78, 95%CI:-1.51, -0.05, $P=0.035$), and tyrosine (β: -0.81, 95%CI:-1.55, -0.06, $P=0.034$) intakes were inversely associated with FTO gene expression in subcutaneous fat tissue. However, no significant associations were observed between the intakes of total AAAs, as well as isoleucine, tryptophan, and phenylalanine, and the expression of either leptin or FTO genes in subcutaneous fat tissue. Furthermore, there were no significant associations found between the intakes of total BCAAs and AAAs and their specific types and the expression of leptin or FTO genes in visceral fat tissue.

Table 1 Demographic characteristics of the participants categorized by their obesity status

Variables	Total ($n=136$)	Overweight-obese Patients (BMI=25–34.9 kg/m^2) ($n=43$)	Morbidly obese patients (BMI≥35 kg/m^2) ($n=93$)	*P*-value*
Age (y)	39.7±12.7	47.0±14.4	36.6±10.5	<0.001
Male (%)	23.5	30.2	20.4	0.210
Physical activity (MET/h/week)	996 (360–1680)	1376 (792–3348)	594 (283–1524)	0.043
Body mass index (kg/m^2)	39.4±8.5	28.6±2.5	44.4±5.0	<0.001
Relative gene expression				
Subcutaneous FTO	7.17±1.77	4.66±2.85	8.33±2.23	0.314
Visceral FTO	1.97±0.51	1.73±0.86	2.08±0.63	0.741
Subcutaneous Leptin	26.59±12.31	30.08±26.72	24.98±13.21	0.865
Visceral Leptin	1.19±0.30	1.21±0.60	1.18±0.34	0.966
Dietary intakes				
Energy (kcal)	3077±1018	2701±898	3252±1028	0.003
Carbohydrate (% of kcal)	55.3±6.3	57.5±6.6	54.3±5.9	0.006
Protein (% of kcal)	13.8±2.4	14.3±2.8	13.6±2.1	0.127
Fat (% of kcal)	30.7±5.9	28.1±5.7	32.0±5.6	<0.001
BCAAs (% of protein)	17.7±0.9	17.7±1.2	17.7±0.7	0.932
Valine (% of protein)	5.4±0.3	5.4±0.4	5.4±0.2	0.962
Leucine (% of protein)	7.8±0.3	7.8±0.5	7.8±0.3	0.919
Isoleucine (% of protein)	4.5±0.2	4.5±0.3	4.5±0.1	0.636
AAAs (% of protein)	9.3±0.3	9.3±0.4	9.3±0.3	0.357
Tryptophan (% of protein)	1.1±0.0	1.1±0.0	1.1±0.0	0.466
Tyrosine (% of protein)	3.5±0.2	3.5±0.1	3.5±0.3	0.720
Phenylalanine (% of protein)	4.6±0.2	4.7±0.2	4.6±0.1	0.055

BCAAs; Branched-chain amino acids, AAAs; Aromatic amino acids, MET; Metabolic equivalents of task

*P-value for between-group analysis was determined by independent samples t-test for normal distributions, Mann-Whitney for skewed distributions, and Chi-square for categorical variables. ($P<0.05$). Data represented as mean±SD or median (IQR 25–75) unless otherwise noted

Table 2 The association of branched-chain and aromatic amino acids (as a percentage of protein) and their components with the expression of FTO and leptin in subcutaneous and visceral fat among 43 overweight-obese patients under bariatric surgery

	FTO.S		FTO.V		Leptin.S		Leptin.V	
	β (95%CI)	*P*-value	β (95%CI)	*P*-value	β (95%CI)	*P*-value	β (95%CI)	*P*-value
BCAAs								
Crude model	-0.55(-1.22– 0.11)	0.104	-0.02 (-0.63–0.58)	0.932	-0.03 (-1.03–0.97)	0.950	-0.23 (-1.14–0.67)	0.600
Adjusted model*	-0.75(-1.47– -0.03)	0.041	0.00 (-0.66–0.67)	0.991	-0.21 (-1.30–0.87)	0.694	-0.26 (-1.26–0.72)	0.588
Valine								
Crude model	-0.59 (-1.27–0.09)	0.088	-0.11 (-0.73–0.50)	0.704	-0.70 (-1.09–0.95)	0.891	-0.48 (-1.40–0.43)	0.295
Adjusted model	-0.78(-1.51– -0.05)	0.035	-0.08 (-0.76–0.59)	0.802	-0.22 (-1.32–0.87)	0.685	-0.51 (-1.50–0.48)	0.305
Leucine								
Crude model	-0.52 (-1.19–0.14)	0.121	0.09 (-0.50–0.70)	0.747	-0.00 (-1.00–0.99)	0.986	-0.17 (-1.08–0.73)	0.702
Adjusted model	-0.72 (-1.44–0.00)	0.051	0.13 (-0.53–0.80)	0.678	-0.19 (-1.28–0.89)	0.719	-0.20 (-1.19–0.79)	0.679
Isoleucine								
Crude model	-0.51 (-1.21–0.18)	0.148	-0.10 (-0.73–0.52)	0.737	-0.00 (-1.04–1.02)	0.987	0.05 (-0.88–1.00)	0.901
Adjusted model	-0.70 (-1.46–0.05)	0.066	-0.10 (-0.79–0.59)	0.771	-0.21 (-1.34–0.91)	0.696	0.04 (-0.99–1.07)	0.933
AAAs								
Crude model	-0.61 (-1.33–0.09)	0.087	0.25 (-0.38–0.89)	0.429	-0.35 (-1.41–0.70)	0.501	-0.59 (-1.54–0.35)	0.211
Adjusted model	-0.72 (-1.47–0.02)	0.056	0.27 (-0.40–0.96)	0.413	-0.50 (-1.60–0.60)	0.360	-0.65 (-1.65–0.34)	0.194
Tryptophan								
Crude model	0.39 (-0.45–1.23)	0.357	0.40 (-0.32–1.14)	0.269	-0.83 (-2.03–0.36)	0.166	0.09 (-1.02–1.21)	0.863
Adjusted model	0.74 (-0.22–1.71)	0.129	0.46 (-0.40–1.32)	0.287	-0.72 (-2.12–0.68)	0.303	0.13 (-1.16–1.43)	0.836
Tyrosine								
Crude model	-0.58 (-1.27–0.10)	0.096	-0.02 (-0.65–0.60)	0.937	-0.12 (-1.15–0.09)	0.804	-0.47 (-1.40–0.44)	0.300
Adjusted model	-0.81(-1.55– -0.06)	0.034	-0.00 (-0.70–0.69)	0.981	-0.39 (-1.51–0.73)	0.485	-0.60 (-1.61–0.41)	0.238
Phenylalanine								
Crude model	-0.67 (-1.45–0.11)	0.092	0.47 (-0.22 −1.17)	0.178	-0.29 (-1.46–0.87)	0.612	-0.67 (-1.71–0.37)	0.203
Adjusted model	-0.74 (-1.56–0.07)	0.073	0.50 (-0.22–1.23)	0.171	-0.36 (-1.58–0.84)	0.542	-0.68 (-1.71–0.41)	0.214

BCAAs; Branched-chain amino acids, **AAAs;** Aromatic amino acids,

*Adjusted for age, sex, physical activity, and energy intake

Table 3 demonstrates the association of BCAAs and AAAs intakes, expressed as a percentage of total protein intake, and their components with the expression of FTO and leptin genes in subcutaneous and visceral fat tissue among morbidly obese patients undergoing bariatric surgery. In models adjusted for confounding variables, higher intakes of BCAAs (β: 1.10, 95%CI:0.07–2.13, $P=0.035$) and leucine (β: 1.07, 95%CI:0.03–2.13, $P=0.044$) were associated with an increased probability of leptin gene expression in subcutaneous fat tissue. Additionally, a higher intake of isoleucine was significantly related to a higher probability of leptin gene expression in subcutaneous fat tissue in both crude and adjusted models (β: 1.45, 95%CI: 0.43–2.48, $P=0.006$, and β: 1.49, 95%CI: 0.46–2.52, $P=0.005$), respectively. However, no significant associations were found between BCAAs or their components and FTO gene expression in subcutaneous fat tissue. Similarly, no significant relationships were observed between the intake of total AAAs or their components and the expression of FTO or leptin genes in subcutaneous fat tissue. Furthermore, the intake of other BCAAs and AAAs did not show any significant relationship with FTO or leptin gene expression in visceral fat tissue.

Discussion

Our findings indicated that in overweight and obese individuals, the intake of BCAAs was inversely related to FTO gene expression in subcutaneous fat tissue. Furthermore, among individuals with morbid obesity, BCAA intake, especially leucine and isoleucine, was positively associated with leptin gene expression in subcutaneous adipose tissue.

The FTO, a nuclear enzyme in the AlkB-related non-heme iron and 2-oxoglutarate-dependent oxygenase superfamily, was associated with BMI, obesity risk, and the development of T2D (Ncbi 2024a). FTO is involved in regulating adipogenesis, energy balance, thermogenesis, and the differentiation of adipocytes into either brown or white fat cells (Jia et al. 2011; Wei et al. 2018; Claussnitzer et al. 2015). Also, leptin, a protein secreted by white adipocytes, acts as an appetite regulator by binding to the leptin receptor (LEPR) in the hypothalamus, reducing food intake and increasing energy expenditure through the promotion of anorexigenic factors and inhibition of orexigenic neuropeptides (NCBI 2024b). Leptin serves endocrine functions, modulating immune and inflammatory responses (Abella et al. 2017) and inhibiting intestinal glucose absorption via the

Table 3 The association of branched-chain and aromatic amino acids (as a percentage of protein) and their components with the expression of FTO and leptin in subcutaneous and visceral fat among 93 morbid obese patients under bariatric surgery

	FTO.S		FTO.V		Leptin.S		Leptin.V	
	β (95%CI)	*P*-value	β (95%CI)	*P*-value	β (95%CI)	*P*-value	β (95%CI)	*P*-value
BCAAs								
Crude model	-0.29 (-1.21–0.62)	0.522	-0.01 (-0.83–0.80)	0.969	0.99 (-0.03–2.01)	0.057	0.43 (-0.40–1.26)	0.306
Adjusted model*	-0.21 (-1.14–0.70)	0.643	0.04 (-0.78–0.88)	0.912	1.10 (0.07–2.13)	0.035	0.46 (-0.38–1.31)	0.275
Valine								
Crude model	-0.41 (-1.29–0.46)	0.350	-0.19 (-0.98–0.59)	0.631	0.70 (-0.28–1.70)	0.161	0.10 (-0.70–0.91)	0.803
Adjusted model	-0.36 (-1.25–0.52)	0.414	-0.13 (-0.94–0.66)	0.732	0.78 (-0.22–1.78)	0.125	0.14 (-0.67–0.97)	0.721
Leucine								
Crude model	-0.30 (-1.22–0.60)	0.505	-0.02 (-0.84–0.79)	0.949	0.88 (-0.14–1.91)	0.091	0.50 (-0.32–1.33)	0.232
Adjusted model	-0.19 (-1.12–0.74)	0.681	0.06 (-0.78–0.90)	0.887	1.07 (0.03–2.12)	0.044	0.54 (-0.31–1.40)	0.209
Isoleucine								
Crude model	0.02 (-0.91–0.96)	0.961	0.32 (-0.51–1.16)	0.438	1.45 (0.43–2.48)	0.006	0.79 (-0.05–1.63)	0.066
Adjusted model	0.06 (-0.87–1.01)	0.885	0.34 (-0.49–1.19)	0.416	1.49 (0.46–2.52)	0.005	0.80 (-0.05–1.65)	0.065
AAAs								
Crude model	-0.46 (-1.30–0.36)	0.266	-0.30 (-1.05–0.44)	0.417	0.29 (-0.65–1.24)	0.544	-0.10 (-0.87–0.66)	0.788
Adjusted model	-0.37 (-1.24–0.48)	0.389	-0.20 (-0.98–0.57)	0.605	0.48 (-0.49–1.47)	0.326	-0.04 (-0.84–0.76)	0.920
Tryptophan								
Crude model	0.16 (-0.67–1.01)	0.692	-0.21 (-0.96–0.54)	0.579	-0.34 (-1.30–0.61)	0.478	-0.29 (-1.06–0.48)	0.452
Adjusted model	0.17 (-0.68–1.02)	0.691	-0.17 (-0.95–0.59)	0.647	-0.29 (-1.26–0.68)	0.551	-0.28 (-1.07–0.50)	0.474
Tyrosine								
Crude model	-0.38 (-1.26–0.49)	0.384	-0.27 (-1.06–0.50)	0.484	0.66 (-0.33–1.65)	0.189	0.24 (-0.55–1.05)	0.544
Adjusted model	-0.31 (-1.20–0.57)	0.479	-0.21 (-1.01–0.59)	0.599	0.78 (-0.22–1.78)	0.126	0.28 (-0.53–1.10)	0.488
Phenylalanine								
Crude model	-0.51 (-1.31–0.29)	0.208	-0.18 (-0.90–0.54)	0.623	-0.02 (-0.94–0.89)	0.955	-0.32 (-1.06–0.41)	0.379
Adjusted model	-0.41 (-1.25–0.43)	0.335	-0.06 (-0.82–0.70)	0.874	0.15 (-0.81–1.12)	0.750	-0.27 (-1.05–0.50)	0.488

BCAAs; c Branched chain amino acids, **AAAs;** Aromatic amino acids,

*Adjusted for age, sex, physical activity and energy intake

PKC pathway, which activates the p38, PI3K, and ERK signaling pathways (El-Zein and Kreydiyyeh 2013). Therefore, changes in FTO and leptin gene expression can impact their functions, with increased FTO expression and decreased leptin expression possibly contributing to the development of obesity (NCBI 2024b; Ncbi 2024a).

Our findings revealed a direct association between dietary BCAA intake and leptin gene expression in individuals with morbid obesity, alongside an inverse relationship between BCAA intake and FTO gene expression in those who are overweight or obese. These outcomes align with earlier studies indicating that monitoring both dietary and serum BCAA levels may serve as valuable indicators for predicting obesity and related complications (Yu et al. 2021; Adams 2011; Xu et al. 2013; Shah et al. 2023; Qin et al. 2011). To our knowledge, few studies have specifically examined the relationship between dietary amino acids and leptin or FTO gene expression. Findings from the Takayama cohort study indicated that increased BCAA intake was linked to a lower risk of T2D (Nagata et al. 2013), with additional benefits in T2D-related factors, such as enhanced insulin sensitivity and improved blood glucose regulation (Layman and Walker 2006). Additionally, Qin et al. reported that middle-aged individuals with high BCAA intake showed a lower prevalence of obesity (Qin et al. 2011). An experimental study suggested that BCAA might increase energy expenditure (D'Antona et al., 2010). Studies in young adults with obesity have also indicated that dietary BCAAs could support muscle protein synthesis and improve glucose metabolism (Liu et al. 2015). Nevertheless, studies reveal that BCAAs function through multiple mechanisms. Their functions include regulating the initiation of protein synthesis (Kimball and Jefferson 2001), providing energy for muscle function (Wagenmakers 1998), modulating insulin/PI3-kinase signaling (Patti et al. 1998; Baum et al. 2005), and supplying nitrogen needed for alanine and glutamine synthesis in skeletal muscle (Ruderman 1975). Additionally, BCAAs serve as key substrates in overall metabolism, exerting a significant influence on energy expenditure (Tobias et al. 2018).

The findings of our study on the inverse association between BCAAs intake and FTO gene expression may be consistent with the results of previous studies that showed the preventive and mediating role of BCAAs in the pathogenesis of obesity and insulin resistance (Serralde-Zúñiga et al. 2014; Huang et al. 2023). Huang et al. revealed that

BCAAs can prevent obesity and adipogenesis by reducing the expression of NADPH-FTO-m6A coordinated manner, which supports a new perspective on the role of m6A in the BCAAs regulation in the prevention of obesity and inhibition of adipogenesis (Huang et al. 2023). Serralde-Zúñiga et al. study has reported that participants with specific genetic variants, such as BCAT2 indicated lower serum levels of BCAAs, and those with the FTO gene variant indicated higher levels of insulin and HOMA-IR than non-IR subjects. This study suggested that adipose tissue dysfunction and occurrence of adiposity is the result of a combination of the presence of some genetic variants, change in adipose tissue gene expression such as FTO, insulin resistance, and change in serum BCAAs levels (Huang et al. 2023).

Studies examining serum BCAA levels have reported potential negative results. Since the balance between dietary BCAA intake and utilization regulates circulating BCAA levels (Neinast et al. 2019), there remain conflicting perspectives in the literature regarding the relationship between BCAA and health outcomes. Elevated serum BCAA levels were associated with an increased genetic risk score for T2D (Wang et al. 2021). Jiang et al. found a strong link between plasma BCAA levels and the risk of diabetes and coronary artery disease, especially in individuals who are obese or have dysglycemia (Jiang et al. 2023). Persistently high plasma BCAA levels have also been identified as predictive factors for insulin resistance and, subsequently, diabetes (De Bandt et al. 2022). Additionally, Wang et al. demonstrated that dietary BCAA intake modulates genetic risk for T2D, showing that individuals with high BCAA consumption had a pronounced association between genetic risk and elevated fasting glucose levels; however, this association diminished with lower BCAA intake (Wang et al. 2021).

Meanwhile, Mahendran et al. utilized a genetic risk score to demonstrate that elevated insulin resistance is associated with increased circulating levels of BCAA, indicating that BCAA may play specific roles across various pathological conditions (Mahendran et al. 2017). Similarly, Adams et al. reported higher serum levels of BCAAs in individuals with obesity or insulin resistance (Adams 2011). It is hypothesized that genes generally implicated in cardiovascular disease and diabetes may also contribute to elevated serum BCAA levels. Genetic analyses have identified two primary pathways associated with increased BCAA levels. The first pathway involves genes related to glucose metabolism, including PPM1K and TRMT61A, which are linked to the progression of atherosclerotic plaque. The second pathway comprises genes associated with neuroendocrine regulation of blood pressure, such as MRPL33, CBLN1, and C2orf16, which are implicated in plaque rupture and thrombosis (Jiang et al. 2023).

Notably, studies indicated that the impact of elevated levels of BCAAs on metabolic health varies depending on mitochondrial metabolic efficiency (Harris et al. 2005). High circulating BCAA levels have been associated with disruptions in their metabolism, primarily due to decreased activity of branched-chain keto acid dehydrogenase (Ruiz-Canela et al. 2016). Doestzada et al. demonstrated that obesity significantly influences the strength and nature of associations between plasma BCAA concentrations and cardiometabolic parameters (Doestzada et al. 2022). Following bariatric surgery and subsequent weight loss, an increase in branched-chain α-keto dehydrogenase activity was observed, along with a significant decrease in blood BCAA levels (Laferrère et al. 2011). This led to the hypothesis that high plasma BCAA levels in obese or diabetic individuals may partly result from reduced BCAA catabolism (Adams 2011). Several studies have indicated decreased activity of BCAA catabolic enzymes in obese, insulin-resistant rodents (She et al. 2007; Doisaki et al. 2010), further emphasizing the link between obesity, insulin resistance, and altered BCAA metabolism. Yoneshiro et al. suggested that exposure to cold temperatures promotes active utilization of BCAAs by brown adipose tissue mitochondria, contributing to thermogenesis and facilitating the clearance of BCAAs from circulation. Conversely, a specific malfunction in BCAA catabolism within brown adipose tissue impairs BCAA clearance, leading to glucose intolerance (Yoneshiro et al. 2019).

This study's strengths include the use of validated, reliable food frequency questionnaires to measure amino acid intake and the examination of gene expression in bariatric surgery patients, offering valuable insights into this specific population. However, this study has some limitations that should be considered that can help shape future research. Given the cross-sectional design, our results do not allow for causal inferences, underscoring the need for cohort studies in this area. Although our sample size was sufficient, financial constraints and the high costs of gene expression analysis limited our ability to study a larger cohort. Future research with larger populations could provide deeper insights into the relationship between dietary amino acids and gene expression. While we minimized measurement bias by using valid and reliable questionnaires, this study, like all observational studies, remains susceptible to such bias.

Conclusions

Our findings suggest that while overall intake of AAAs did not show a significant association with leptin and FTO gene expression, higher dietary intake of BCAAs demonstrated

an inverse association with FTO gene expression in overweight-obese individuals and a positive association with leptin expression in morbidly obese individuals. These results imply that dietary BCAAs could serve as an indicator for leptin and FTO gene expression in subcutaneous adipose tissue and suggest a potential role for BCAAs in the recovery process for diabetic and obese individuals. However, these findings are preliminary, and further prospective studies are needed for confirmation.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The written informed consent form was obtained from volunteer patients before their inclusion in the study, and a blood sample was taken from each participant before surgery. All participant information was kept confidential by the research team. All procedures involving human participants adhered to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was assessed and approved by the ethics research committee of the National Institute for Medical Research Development (NIMAD), Tehran, Iran.

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