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Dietary Intakes of Branched Chain Amino Acids and the Incidence of Hypertension: A Population-Based Prospective Cohort Study

Parvin Mirmiran, PHD[1]; Farshad Teymoori, PHD[1,2]; Golaleh Asghari, PHD[3*]; Fereidoun Azizi, MD[4]

[1]Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

[3]Student Research Committee, Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: Dietary amino acids have been associated with blood pressure (BP) in previous studies; we conducted this study to examine the association between dietary branched chain amino acids (BCAAs) and the incidence of hypertension among participants of the Tehran Lipid and Glucose Study (TLGS).

Methods: Analyses were conducted on 4,288 participants aged 20–70 years, who were free of hypertension at baseline (2008–2011) and were followed for 3 years (2011–2014) to ascertain incident hypertension. Dietary intakes of BCAAs including, valine, leucine, and isoleucine were collected at baseline using the food frequency questionnaire (FFQ). Odds ratio (OR) of hypertension were determined by logistic regression across quartiles of BCAAs, adjusted for sex, age, smoking status, physical activity, body mass index (BMI), diabetes, and some dietary factors.

Results: The mean ± standard deviation for age and BMI of participants (41.9% men) were 39.7 ± 12.8 years and 26.9 ± 4.6 kg/m^2, respectively. The median intakes of total BCAAs, valine, leucine, and isoleucine was 17.9, 5.5, 7.8, and 4.5 percentage of total amino acids intake, respectively. We documented 429 (10%) hypertension incident cases. The multivariable adjusted OR for the highest vs lowest quartiles of BCAAs was 1.54 (95% confidence interval (CI):1.03–2.32; *P* for trend = 0.05); furthermore, the OR (95% CI) of hypertension for the highest vs the lowest quartile of valine was 1.61 (1.10–2.36; *P* for trend = 0.009) in the fully adjusted model. However, we found no significant association between leucine and isoleucine with incidence of hypertension.

Conclusion: Findings indicated that higher BCAA intake, in particular valine, is associated with higher risk of incident hypertension.

Keywords: Branched chain amino acids, Hypertension, Isoleucine, Leucine, Valine

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Introduction

Hypertension is one of the main public health challenges worldwide and is a major risk factor for cardiovascular and chronic kidney disease.[1] The estimated total number of hypertensive adults in 2000 was 972 million and it is predicted that this number in 2025 would increase by about 60% to a total of 1.56 billion.[2]

Recently, much research is being focused on the association of amino acids with blood pressure (BP). In the International Study of Macronutrients and Blood Pressure (INTERMAP study), higher intakes of glutamic acid and glycine were related to lower and higher blood pressure, respectively.[3,4] Branched chain amino acids (BCAAs) including leucine, isoleucine, and valine are essential amino acids, which contribute to several body activities such as protein synthesis, glucose metabolism, and regulation of some pivotal pathways.[5,6] High BCAA levels have been reported in some chronic diseases such as liver failure, obesity, insulin resistance, diabetes, and cardiovascular disease.[5,7-10] Similarly, Yanagisawa et al reported that levels of BCAAs and aromatic amino acids (AAAs) in pulmonary hypertension were raised and fisher ratios (BCAAs/AAAs) decreased.[11] There are limited studies on the association of dietary BCAA intake with chronic disease., Two of these studies, which investigated the relation of BCAA intake and diabetes incidence, showed controversial findings.[12,13] Since BCAA levels are associated with different chronic diseases, viz insulin resistance and obesity, and insulin resistance is also associated with high BP, it is more likely that BCAAs are also related to hypertension. Furthermore, many questions on the observed relation between protein intake and BP may be explained by amino acid profiles.[14] We hypothesized that BCAAs may play a role in incident hypertension.

***Corresponding Author:** Golaleh Asghari, MD; Nutrition and Endocrine Research Center, Research Institute for Endocrine Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran. P.O. Box: 19395-4763; Phone: +98 (21) 22432503; Fax: +98 (21) 22402463; Email: g_asghari@hotmail.com; Asghari@endocrine.ac.ir

In the present study, we prospectively analyzed the association of dietary intakes of total BCAAs, valine, leucine, and isoleucine with incidence of hypertension in adult participants of the Tehran Lipid and Glucose Study (TLGS).

Materials and Methods

Subjects

This study, conducted within the framework of TLGS, which is a population based prospective study aimed to determine risk factors of non-communicable disease and to reduce these risk factors; details have been reported previously.[15] This ongoing study at baseline phase began in 1999 and data collection from 15 005 subjects, aged >3 years was performed to 2001. Data were collected prospectively at three-year intervals; phase 2 (2002–2005), phase 3 (2005–2008), phase 4 (2008–2011), and phase 5 (2011–2014). From 12823 participants in the fourth phase, 7956 subjects were randomly selected to complete the dietary assessment.

For the present study, a total of 6493 participants aged 20–70 years with complete data from the fourth phase of TLGS were enrolled and followed up to fifth phase (median follow-up: 3.1 years). After exclusion of participants, who under or over–reported dietary intakes (<800 kcal/d or >4500 kcal/d, respectively) (n = 317), those with history of myocardial infraction, cerebral vascular accidents, and cancers (n = 43), and hypertensive ones (n = 1057), lactating and pregnant women (n = 106), finally 5004 subjects with normal BP remained. After 3.1-year follow-up, data of 4315 participants were considered for the final analysis (follow up rate: 86.2%).

Dietary Intake Assessment

To assess dietary intakes of participants, we used a valid and reliable semi-quantitative food frequency questionnaire (FFQ).[16] During face-to-face interview, consumption frequency for each food item during the previous year on a daily, weekly, or monthly basis of participants was collected by trained and experienced dieticians. Portion sizes of consumed foods, reported in household measures were then converted to grams. Using the United States Department of Agriculture (USDA) food composition table (FCT), energy and nutrients content were computed. For local food items that were not available in USDA FCT, The Iranian FCT[17] was used. Data on amino acids was calculated using USDA (USDA National Nutrient Database for Standard Reference, Release 28) FCT of 2015 (http://www.ars.usda.gov/ba/bhnrc/ndl), which is based on the chemically analyse of amino acids composition of over 5000 food items from all food groups. Dietary intakes during the fourth phase (2008–2011) assessment of TLGS were considered as dietary intake exposure at baseline.

Daily intakes of leucine, valine, isoleucine, and total BCAAs were compared to estimated requirement in healthy adults, which were reported as 40, 17–25, 19, and 84 mg/ kg body weight, respectively.[18]

Physical Activity Assessment

To estimate physical activity levels, the Modifiable Activity Questionnaire, modified and validated previously among Iranians, was used.[19] Individuals were asked to report and identify the frequency and time spent during the past 12 months on activities of light, moderate, hard, and very hard intensity, according to a list of common activities of daily life; physical activity levels were expressed as metabolic equivalent hours per week (MET-h/wk).

Clinical and Biological Measurements

Information on age, sex, medical history, medication use, and smoking habits of participants were collected by trained interviewers, using pretested questionnaires. Anthropometric measures including weight, height, and waist circumference (WC) were measured, and body mass index (BMI) was computed. Weight was measured with light clothing and accuracy of up to 100 g using a SECA digital weighing scale (Seca 707; Seca Corporation, Hanover, Maryland; range, 0.1–150 kg). Height measurement conducted while participants were in standing position, without shoes and shoulders in normal alignment, using a stadiometer with a minimum measurement of 1 mm. BMI was calculated as weight in kilograms, divided by height in meters squared. WC was measured to the nearest 0.1 cm using an unstretched shape tape meter, on the level of the umbilicus, over light clothing, without any pressure to body surface. Measurement of BP was conducted twice on the right arm after resting for at least 15-minute sitting on chair, with a minimum interval of 30 seconds, using a mercury sphygmomanometer and Korotkoff sound technique, with an accuracy of 2 mm Hg; the average of two measurements was considered as the final pressure; systolic BP was determined with onset of the first sound heard and diastolic blood pressure (DBP) with disappearance of the sound. All subjects' blood samples were collected after a 12 to 14 hours of overnight fast in a sitting position between 7:00 and 9.00 AM, intermediately, centrifuged within 30–45 minutes of collection. All blood samples were analysed at the TLGS research laboratory on the day of blood collection by using of Selectra 2 auto-analyzer (Vital Scientific, Spankeren, the Netherlands). Triglyceride (TG) levels were measured using the enzymatic calorimetric method with glycerol phosphate oxidase. Inter- and intra-assay CVs for TGs were 0.6 and 1.6%, respectively. Serum high-density lipoprotein-cholesterol (HDL-C) was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid. Enzymatic colorimetric tests were used to assay total cholesterol (TC) with cholesterol esterase and cholesterol oxidase. Inter- and intra-assay CVs for both TC and HDL-C were 0.5 and 2% respectively.

Friedewald formula were used to calculate low-density lipoprotein-cholesterol (LDL-C) and expressed in mg/dL, analyses performed using commercial kits (Pars Azmoon Inc., Tehran, Iran).

Definitions

Hypertension was determined according to the Eighth Joint National Committee (JNC 8) criteria, which has been defined separately for subjects aged < 60 years and ≥ 60 years[20]: systolic blood pressure (SBP) ≥ 140 mm Hg, DBP ≥ 90 mm Hg, or taking antihypertensive medications for subjects aged < 60 years and SBP ≥ 150 mm Hg, DBP ≥90 mm Hg or taking antihypertensive medications for those aged ≥ 60 years. Diabetes defined as participants who had fasting plasma glucose (FPG) ≥126 mg/dL or 2-hour post 75 g glucose load ≥200 mg/dL or were currently on medication therapy for diagnosed diabetes based on American Diabetes Association criteria.[21]

Smoking status defined as smokers (subjects who smoke cigarettes daily or occasionally) and non-smokers.

Statistical Analysis

Amino acids intake was reported as percentage of total amino acids intake and categorized into quartiles. Data analyses were conducted using Statistical Package for Social Sciences (version 15.0; SPSS Inc, Chicago IL). We used Kolmogorov-Smirnov analysis and histogram charts for assessing the normality of variables. The correlation coefficients between leucine, valine, and isoleucine were measured using Spearman correlation test.

Baseline characteristics of subjects were expressed as mean ± SD or median (25–75 interquartile range) for continuous variables, and percentages for categorical variables across quartiles of BCAAs intake. Chi-square and linear regression were used to test the trend of qualitative and quantitative variables across quartiles of BCAAs (as median value in each quartile), respectively. Participants were categorized according to quartiles of BCAAs (based on percentage of total amino acids intake) cut off points. Multivariable logistic regression were used to estimate risk of 3-year incident hypertension with quartiles of BCAAs as independent variable; odds ratio (OR) and 95% confidence interval (CI) were reported. Logistic regression models were adjusted for sex, age, smoking status, physical activity, BMI, diabetes, dietary intakes of energy, carbohydrate, fat, saturated fatty acid (SFA), polyunsaturated fatty acid (PUFA), calcium, magnesium, sodium, potassium, and fiber. Further adjustment for mutual amino acids was also conducted. *P*-values < 0.05 were considered as statistically significant.

Results

The median (25–75 IQR) for BCAA intake was 14.0 (11.7–17.9) g/d which corresponds to 17.9 (17.3–18.5) percent of total amino acids intake. The highest contribution of BCAAs pertained to leucine (44%), followed by valine (31%) and isoleusine (25%). The mean dietary intakes of leucine, valine, isoleucine, and total BCAAs based on mg/kg body weight was 91, 64, 52, and 207, respectively, which are more than two times higher than estimated requirements.

The unadjusted Spearman correlation coefficients between dietary intake of individual amino acids were 0.82 (for valine and isoleucine), 0.89 (for leucine and isoleucine), and 0.92 (for leucine and valine). BCAAs intake had higher correlation with protein from animal sources (0.86) than from that with vegetable sources (0.65). After three years of follow-up, a total of 429 (10%) incident cases of hypertension (49.9% men) were ascertained.

Baseline characteristics of study participants according to quartiles of BCAAs are presented in Table 1, showing that across quartiles of BCAAs, HDL-C and intakes of total and animal protein, fat, SFA, and calcium increased (P < 0.04), whereas the number of male participants, intakes of energy, carbohydrate, plant protein, PUFA, sodium, magnesium, and fiber decreased (P < 0.01). There was no significant difference for age, diabetes, BMI, smoking, physical activity, SBP, DBP, LDL-C, TGs, cholesterol, dietary intakes of total protein, fat, and potassium across quartiles of BCAAs intake (all P for trend > 0.05)

The associations between BCAA intakes and incidence of hypertension are shown in Table 2. The OR (95% CI) of the highest vs the lowest quartile of BCAAs intake (19% of protein, compared to 17%) were 1.54 (95% CI: 1.03–2.32; P for trend = 0.050) in the fully adjusted model. Subjects in the highest quartile intake of valine had 61% higher risk of incident hypertension (OR = 1.61; 95% CI:1.10–2.36; P for trend = 0.009) after adjusting for age, sex, BMI, physical activity, smoking, diabetes, intakes of energy, carbohydrates, fat, SFA, PUFA, fiber, calcium, magnesium, sodium, and potassium. The OR (95% CI) for valine was 2.26 (1.25–4.07) after mutual adjustment of amino acids (P for trend = 0.006). Our data did not show significant associations of leucine and isoleucine with incident hypertension.

Discussion

Higher intakes of BCAAs were related to higher risk of incident hypertension in the fully adjusted model. In individual analyses for three BCAAs, we observed that greater intake of valine was associated with higher incidence of hypertension - an association which was more significant after addition adjustment for mutual amino acids. Our data, however, indicated no significant association between leucine and isoleucine intake and the risk of hypertension.

BCAAs have similar structure and cellular transporter system and they are in high harmony together in pathophysiology of related morbidities, indicating an

Table 1. Baseline Characteristics of Participants According to Quartiles of Branched Chain Amino Acid Intake

	Quartiles				*P* for Trend*
	Q1 (n = 1072)	Q2 (n = 1072)	Q3 (n = 1072)	Q4 (n = 1072)	
Age (y)	40.1 ± 12.2	39.1 ± 12.1	38.5 ± 11.8	39.3 ± 11.9	0.081
Men (%)	42.9	45.9	44.3	35.4	<0.001
Diabetes (%)	4.8	5.7	5.5	4.6	0.753
Body mass index (kg/m^2)	26.9 ± 4.6	26.8 ± 4.4	26.6 ± 4.6	27.0 ± 4.5	0.952
Smoking (%)	10.5	12.8	10.9	9.9	0.508
Systolic blood pressure (mm Hg)	111.7 ± 13.7	111.7 ± 14.2	111.0 ± 13.6	111.7 ± 14.2	0.848
Diastolic blood pressure (mm Hg)	75.3 ± 9.0	75.3 ± 8.9	75.0 ± 8.9	75.4 ± 9.2	0.902
Physical activity (MET/h/wk)	62.5 (24.4–94.1)	61.0 (28.4-93.5)	62.3 (26.7-103.5)	56.3 (23.8-88.3)	0.066
LDL-cholesterol (mg/dL)	110.7 ± 33.7	108.6 ± 31.8	111.2 ± 33.1	110.1 ± 30.1	0.919
HDL- cholesterol (mg/dL)	47.8 ± 11.6	47.4 ± 11.2	47.9 ± 11.5	48.7 ± 11.9	0.049
Triglycerides (mg/dL)	112 (81-65)	112 (79-164)	109 (78-155)	115 (79-162)	0.486
Cholesterol (mg/dL)	185.5 ± 38.6	182.6 ± 36.7	184.3 ± 37.7	185.3 ± 35.4	0.823
Dietary intakes					
Energy(kcal)	2566 ± 793	2481 ± 744	2397 ± 708	2254 ± 719	<0.001
Total protein (% of energy)	12.8 ± 3.0	13.6 ± 2.3	14.0 ± 2.4	14.6 ± 2.1	<0.001
Total protein (g)	82.3 ± 30.4	84.3 ± 29.3	84.2 ± 28.9	81.8 ± 27.7	0.605
Plant protein (% of energy)	7.7 ± 2.0	7.0 ± 1.3	6.5 ± 1.3	6.0 ± 1.3	<0.001
Plant protein (g)	49.4 ± 19.3	43.8 ± 15.7	39.4 ± 14.7	33.8 ± 12.6	<0.001
Animal protein (% of energy)	5.1 ± 2.2	6.5 ± 2.3	7.4 ± 2.5	8.5 ± 2.2	<0.001
Animal protein (g)	32.8 ± 17.5	40.3 ± 19.8	44.6 ± 20.9	47.9 ± 20.1	<0.001
Total fat (% of energy)	28.2 ± 6.2	29.9 ± 6.1	30.9 ± 5.9	31.3 ± 6.0	<0.001
Total fat (g)	80.6 ± 32.0	82.7 ± 30.5	82.7 ± 29.9	79.3 ± 32.8	0.277
SFA (% of energy)	8.1 ± 2.3	9.4 ± 2.3	10.3 ± 2.6	11.4 ± 2.7	<0.001
SFA (g)	23.3 ± 10.0	25.9 ± 10.0	27.6 ± 10.8	28.8 ± 12.7	<0.001
PUFA (% of energy)	5.9 ± 2.0	6.1 ± 2.0	6.0 ± 1.9	5.7 ± 1.8	0.016
PUFA (g)	17.0 ± 8.1	16.8 ± 7.3	16.1 ± 7.0	14.6 ± 7.2	<0.001
Carbohydrates (% of energy)	62.2 ± 6.5	58.9 ± 6.4	57.1 ± 6.0	55.9 ± 5.8	<0.001
Carbohydrates (g)	399.3 ± 131.7	364.9 ± 115.2	342.0 ± 107.3	314.0 ± 99.7	<0.001
Sodium (mg/1000 kcal)	1549 ± 457	1545 ± 464	1525 ± 469	1483 ± 405	<0.001
Potassium (mg/1000 kcal)	1979 ± 603	1903 ± 541	1915 ± 501	2010 ± 516	0.137
Magnesium (mg/1000 kcal)	205 ± 43	195 ± 40	191 ± 37	192 ± 37	<0.001
Calcium (mg/1000 kcal)	533 ± 188	577 ± 186	626 ± 172	748 ± 198	<0.001
Fiber (g/1000 kcal)	18.7 ± 6.8	16.2 ± 6.3	14.8 ± 7.3	13.4 ± 6.0	<0.001

LDL-cholesterol, low-density lipoprotein-cholesterol; HDL- cholesterol, high-density lipoprotein-cholesterol; SFA, saturated fatty acid; PUFA, poly unsaturated fatty acid; Q, quartile.
Data represented as mean ±SD, or median (IQR 25-75).
* Chi-square and linear regression were used to test the trend of qualitative and quantitative variables across quartiles of BCAAs (as median value in each quartile), respectively.

alignment and coordinated manifestation of different conditions in the human body. Today, BCAAs are often considered as a single unit in studies of several diseases and in practical and operational complementary therapies in different groups such as athletes. It seems likely that their interaction is inevitable, so it was thought that assessing the BCAAs as a unit would give a better, more rational, and deeper insight about their actual behaviour in the human body, and it may be the justification for other studies to evaluate BCAAs as an independent unit in the BCAA-disease relationship. Recently, BCAAs are attracting much attention for their association with chronic diseases[5,7,10,12,13,22]; most studies focused on plasma BCAA concentrations[5,7,10,11] rather than dietary intakes.[12,13]

Higher dietary intakes of BCAA showed different associations with diabetes in two cohort studies.[12,13] To the best of our knowledge, no previous study had investigated the association of BCAAs and incident hypertension. In a cross-sectional study in female twins, higher leucine intake was associated with lower SBP, not DBP[14]; however, in our study with a cohort design and in both males and females, leucine intake had no association with incident hypertension- a divergent finding which may be due to differences in study design and participant gender between the two studies.

Whey protein, a rich source of BCAAs, has been investigated in relation to BP and indicated inconsistent associations with BP.[23-25] Some studies showed antihypertensive effects of whey protein and considered it as a heterogeneous group of proteins, especially lactokinins, recognized as the whey-derived peptide inhibitors of the angiotensin converter enzyme.[23,25] However, administration of whey protein supplementation at low (2.6 g/d) and high (45 g/d) dosages did not show any effects on reduction of BP.[24,25] As BCAAs seem to have hypertensive effects, it is possible that high contents of BCAAs in whey protein

Table 2. Adjusted odds ratios (95% confidence interval) of incident hypertension across quartiles of branch amino acids (BCAAs)

	Quartiles				*P* for Trend
	Q1 (*n* = 1072)	Q2 (*n* = 1072)	Q3 (*n* = 1072)	Q4 (*n* = 1072)	
Total BCAAs					
Median	17.00 (16.66 – 17.20)	17.66 (17.53 – 17.81)	18.21 (18.07 – 18.35)	19.00 (18.73 – 19.44)	
Model 1[a]	1.00 (Ref)	1.23 (0.92 – 1.64)	1.11 (0.82 – 1.50)	1.24 (0.93 – 1.67)	0.212
Model 2[b]	1.00 (Ref)	1.24 (0.92 – 1.68)	1.14 (0.84 – 1.54)	1.23 (0.91 – 1.65)	0.226
Model 3[c]	1.00 (Ref)	1.33 (0.97 – 1.82)	1.29 (0.91 – 1.84)	1.54 (1.03 – 2.32)	0.050
Valine					
Median	5.16 (5.07 – 5.25)	5.42 (5.37 – 5.47)	5.64 (5.58 – 5.70)	5.98 (5.86 – 6.16)	
Model 1[a]	1.00 (Ref)	1.04 (0.77 – 1.40)	1.20 (0.89 – 1.61)	1.26 (0.94 – 1.68)	0.076
Model 2[b]	1.00 (Ref)	1.07 (0.79 – 1.46)	1.24 (0.92 – 1.68)	1.27 (0.94 – 1.71)	0.072
Model 3[c]	1.00 (Ref)	1.18 (0.86 – 1.62)	1.43 (1.02 – 1.99)	1.61 (1.10 - 2.36)	0.009
Model 4[d]	1.00 (Ref)	1.29 (0.92 – 1.82)	1.74 (1.14 – 2.67)	2.26 (1.25 – 4.07)	0.006
Leucine					
Median	7.46 (7.30 – 7.55)	7.75 (7.69 – 7.81)	7.97 (7.92 – 8.03)	8.29 (8.19 – 8.48)	
Model 1[a]	1.00 (Ref)	1.10 (0.82 – 1.48)	1.16 (0.87 – 1.56)	1.16 (0.86 – 1.55)	0.285
Model 2[b]	1.00 (Ref)	1.08 (0.80 – 1.46)	1.22 (0.90 – 1.65)	1.14 (0.84 – 1.54)	0.308
Model 3[c]	1.00 (Ref)	1.18 (0.85 – 1.62)	1.39 (0.98 – 1.97)	1.42 (0.94– 2.14)	0.074
Model 4[d]	1.00 (Ref)	1.00 (0.69 – 1.46)	1.02 (0.60 – 1.71)	0.89 (0.44 – 1.80)	0.723
Isoleucine					
Median	4.30 (4.22 – 4.35)	4.48 (4.44 – 4.51)	4.60 (4.56 – 4.63)	4.76 (4.71 – 4.85)	
Model 1[a]	1.00 (Ref)	1.16 (0.87 – 1.55)	1.04 (0.78 – 1.40)	1.05 (0.78 – 1.40)	0.879
Model 2[b]	1.00 (Ref)	1.18 (0.88 – 1.59)	1.10 (0.81 – 1.48)	1.04 (0.77 – 1.40)	0.874
Model 3[c]	1.00 (Ref)	1.19 (0.86 – 1.63)	1.11 (0.77 – 1.59)	1.07 (0.69 – 1.66)	0.784
Model 4[d]	1.00 (Ref)	0.94 (0.66 – 1.35)	0.72 (0.45 – 1.15)	0.59 (0.32 – 1.07)	0.078

[a] Adjusted for age and sex.
[b] Additionally adjusted for diabetes, body mass index, physical activity, smoking (yes or no), and daily energy intake.
[c] Additionally adjusted for carbohydrates, fat, saturated fatty acids, poly unsaturated fatty acids, fiber, calcium, magnesium, sodium, and potassium (all continuous).
[d] Additionally adjusted for mutual branched chain amino acids.

interacts with beneficial components of whey, neutralizes its antihypertensive effects, and could be a justification for disappearance of beneficial effect of whey protein supplementation on BP.

Elevated levels of BCAAs have been reported in several chronic diseases such as insulin resistance, diabetes, cardiovascular disease, and also pulmonary hypertension.[10,11,13] It has been shown that BCAA supplementation substantially elevates BCAA levels.[26] It has been demonstrated that after consumption of mixed diet, especially high protein diets, BCAAs (leucine and valine) were more elevated in plasma than other amino acids.[27] It is also reported that 80% of ingested dietary BCAAs entered in the blood circulation.[28] About 50% of leucine and isoleucine and 60% of valine plasma levels are influenced by diet.[29] Previous studies show a correlation between BCAA intakes and plasma levels; higher intakes of BCAA had a moderate correlation with higher plasma BCAA levels[13] and also calculated amino acid intakes from FFQ and food records, correlated with plasma amino acid levels.[30,31]

It is probable that some physiological functions are involved in the association between high BCAA intake and hypertension. High levels of BCAAs and their metabolites such as glutamine and alanine as glucogenic amino acids stimulate insulin secretion. Furthermore, BCAA catabolism product accumulation, including propionyl CoA and succinyl CoA, which contribute to incomplete lipid oxidation, may lead to chronic hyperinsulinemia and consequently cell dysfunction and insulin resistance.[32] The association of BCAAs and insulin resistance has been recognized previously[2,33,34] similar to the relation between insulin resistance and hypertension in some other studies[35,36]; it may also be a potential mechanism related to our findings. It has also been reported that higher intakes or plasma levels of BCAAs can reduce brain tryptophan and consequently brain serotonin[10,37] - a reduction of serotonin affects the nervous system and has adverse effects on BP.

Food supply of BCAAs, despite similar amounts, may contribute to different associations of BCAAs with chronic diseases.[12,13] Higher BCAA intake was related to lower incidence of diabetes in the Takayama Study, the main sources of which were cereals, potatoes, starches (23–25%), fish, shellfish (21%–23%) and meats (14%–15%).[13] However, higher BCAA intakes in a recent study, supplied more from meats (37%), fish (8%), and milk (12%) was associated with higher incident diabetes.[13] Main sources of BCAA intakes in our study were dairy products (31.5%), followed by cereal (29%), meats (20.5%), and fish (3.4%). In our study, BCAAs, supplied 57.2% by animal protein sources, had high correlation (0.86) with animal sources and showed an adverse association with hypertension. Therefore, the correlation of BCAAs with animal sources

could be an explanation for our findings. Furthermore, our results, though small, might help to justify the previously reported associations between animal protein and BP.[38,39]

Our study does however have its limitations. First, due to lack of data on serum amino acid concentrations, we could not measure the correlation between dietary intake and serum levels of BCAAs; therefore, we could not provide a logical interpretation of the association between dietary BCAAs and incident hypertension. Second, the effects of some residual confounding variables may have occurred although we adjusted a wide variety of potential confounders. The main strengths of our study were its cohort design, which infers a causal relationship. Furthermore, this is a population based study with a large sample size and a wide age range (20–70 years), which is representative of the general population; and last, but not least, the use of no self-administered dietary intake questionnaire or self-reported BP.

In conclusion, our data indicated a positive significant association between higher dietary intakes of total BCAAs, in particular valine, and incident hypertension adjusted for potential confounders. More studies are required to elucidate the potential role of BCAAs in hypertension.

Authors' Contribution

PM conceptualized and designed the study. GA and FT analysed and interpreted the data. GA, FT, and PM drafted the initial manuscript. FA supervised the project and approved the final version of the manuscript as submitted.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

The study was approved by the ethics committee of the Research Institute for Endocrine Sciences, affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. Written informed consent was obtained from all participants.

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