Association between type 2 diabetes and branched chain amino acids (BCAA); a case-control study

Saheb Abbas Torki[1], Effat Bahadori[2], Zohreh Aghakhaninejad[3], Golsa Khalatbari Mohseni[4], Shirin Tajadod[5], Asma Rajabi Harsini[6], Fatemeh Azaryan[7], Zahra Saeedirad[8], Seyed Ali Askarpour[9], Zahra Mahmoudi[10], Sara Khoshdooz[11], Bojlul Bahar[12], Hanieh Shafaei[13], Seyed Alireza Mosavi Jarrahi[14], Saeid Doaei[15], Samad Nazemi[16], Maryam Gholamalizadeh[17]

[1] Department of Nutrition, Faculty of Nutrition Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

[2] Department of Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran

[3] Department of Nutrition, Faculty of Public Health, Kerman University of Medical Sciences, Kerman, Iran

[4] Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[5] Department of Nutrition, School of Public Health, International Campus, Iran University of Medical Sciences, Tehran, Iran

[6] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

[7] Department of Physiology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

[8] Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[9] Division of Food Safety and Hygiene, Department of Environmental Health Engineering, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

[10] Department of Nutrition, Science and Research Branch, Islamic Azad University, Tehran, Iran

[11] Guilan University of Medical Sciences, Rasht, Iran

[12] Nutrition Sciences and Applied Food Safety Studies, Research Centre for Global Development, School of Sport and Health Sciences, University of Central Lancashire, Preston, UK

[13] Nursing and Midwifery School, Guilan University of Medical Sciences, Rasht, Iran

[14] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[15] Department of Community Nutrition, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of

Medical Sciences, Tehran, Iran
[16] Cellular and Molecular Research Center, Department of Physiology and Pharmacology, Sabzevar University of Medical Science, Sabzevar, Iran
[17] Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background Several amino acids and their derivatives have been implicated in insulin resistance (IR) and Type 2 Diabetes Mellitus (T2DM). This research sought to establish a relationship between the dietary levels of branched-chain amino acids (BCAA) and the risk of T2DM.

Methods This case-control study was carried out on 4200 participants consisting of 589 people with T2DM and 3611 non- diabetic aged 35 to 70 years residents in Sabzevar, Iran. Data on the economic-social, employment status, medical history, lifestyle, and sleep habits were collected via interview. The food frequency questionnaire (FFQ) was used to check the nutritional status. Participants' dietary BCAA consumption was estimated using Nutritionist IV software.

Results A significant negative association between the incidence of T2DM and the dietary levels of BCAAs after adjustment for age and sex (OR = 0.972, CI 95%:0.648–0.996, P= 0.022). The negative association remained significant after additional adjustments for body mass index (BMI) and physical activity (OR = 0.967, CI 95%: 0.943–0.992, P= 0.010). Interestingly,
a positive association was found between T2DM and total BCAAs (OR = 1.067, CI 95%: 1.017–1.119, P= 0.008), Isoleu- cine (OR = 1.248, CI 95%: 1.043–1.494, P= 0.016), Leucine (OR = 1.165, CI 95%: 1.046–1.299, P= 0.006) and Valine
(OR = 1.274, CI 95%: 1.088–1.492, P= 0.003) after further adjustment for calorie intake.

Conclusions Our results demonstrate branched-chain amino acids (BCAAs) including isoleucine, leucine, and valine are negatively associated with the incidence of type 2 diabetes (T2DM) after adjusting for age and sex, BMI, and physical activity. However, adjusting for calorie intake reversed the association between T2DM and BCAAs. These findings suggest that the association between BCAAs and T2DM may be influenced by calorie intake. Future longitudinal studies are warranted.

Keywords Type 2 diabetes mellitus · Branched-chain amino acids · Dietary intake

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders that affect a large part of the population, and based on World Health Organization (WHO), the number of the adult population living with diabetes is expected to rise to 693 million by 2045 [1]. T2DM is a multifactorial chronic disease brought on by a mix of reversible risk fac- tors including a poor diet and inactivity as well as irreversible risk factors like genetics, age, race, and ethnicity [2, 3]. Several dietary patterns were connected to the development of type 2 diabetes, however, the ideal macronutrient profile that can reduce the risk of diabetes is still to be established [4] The restriction of the carbohydrate content in the meal was shown as an important factor to reduce postprandial glycemia [5]. An increase in fat and protein in the diet with a moderate reduction in carbohydrates was reported to reduce postprandial glucose and improved T2DM control [6]. On the other hand, higher consumption of total protein, particularly from animal sources was associated with an increased risk of diabetes [7–10], while a diet high in plant protein was associated with a decreased risk [11]. The roles of different amino acids and their derivatives in IR and T2DM were extensively investigated [12–19]. The BCAA – Isoleucine, Leucine, and Valine – have specific structural features (non-linear aliphatic side chain) due to which they have identical catabolic pathways. BCAA are essential amino acids, which cannot be synthesized de novo, and dietary intake is the only source [20]. A typical diet con- sists of 15–25% BCAA [21] and the plasma BCAA levels increase following consumption of a meal with BCAA, which is reported to be associated with an increased risk of T2DM [20]. Hence, the BCAA metabolism and plasma concentration are reliable markers of insulin action and can be used to predict the risk of developing obesity and T2DM [22].

While the BCAA represent essential amino acids required for cellular protein synthesis, there is conflicting evidence available to support their role in the metabolic health [23–25]. For instance, a Leucine-rich diet was reportedly associated with a lower incidence of obesity and metabolic syndrome [26]. In the mice model, an increase in the dietary Leucine intake substantially decreased diet-induced obesity, hyperglycemia, and hypercholesterolemia [23] Although the attempt to understand the role of BCAA in metabolic health dates back to 1976, their role in T2DM is still to be elucidated [24]. Therefore, this case-control study aimed to investigate the association of dietary intake of BCAA with the risk of T2DM.

Methods

Study population

This case-control study was carried on a total of 4200 participants of the first phase of the Persian

Sabzevar Cohort Study (PSCS), consisted of 589 patients with T2DM and 3611 non-diabetic people aged 35 to 70 years in Sabzevar, Iran. For this study, T2DM was defined as fasting blood sugar equal to or higher than 126 mg/L. Inclusion criteria were age between 35 and 70 years, no more than 3 months have passed since the diagnosis of diabetes in the cases, and written consent to participate. Exclusion criteria include people with a family history of diabetes, undergoing treatment with drugs affecting diabetes, and current use of branched-chain amino acid supplements.

Data collection

Data on economic-social and employment status, lifestyle, and sleep habits were collected. Furthermore, drug history, medical history, and hospitalization status in the last year were collected during the interview. The level of physical activity was measured as the metabolic equivalent of task (MET). A MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest. To measure weight and height, a mechanical column scale (SECA 755) and a mobile stadiometer (SECA204) were used, respectively. The BMI of the participants was calculated using the following formula: body weight(kg)/height(m)^2 [1]. Furthermore, to check the nutritional and supplement status, the data was obtained from the Persian cohort food frequency questionnaire (FFQ), and its validity and reliability were confirmed. Then, the participant's dietary BCAA consumption was estimated using Nutritionist IV software.

At the time of the examination, blood samples were taken from the antecubital vein for biochemical analysis after an overnight fast of at least 10 h, and the serum was separated and maintained at a temperature of -70^0 C. Diabetes was diagnosed at fasting blood sugar (FBS) of greater than or equal to 6.99 mmol/L (126 mg/dL), according to the Ameri- can Diabetes Association 2020 criteria [25].

Statistical analysis

The data on the variables measured were analyzed, and for the quantitative variables, means were compared between the two groups by an independent t-test or non-parametric (Mann-Whitney) test. For the qualitative variables, the two groups were compared by Chi-square test. The association between T2DM and dietary intake of BCAA was assessed using different models of logistic regression. All analyses were performed using SPSS software and $P< 0.05$ was considered as the cut-off for the statistical probability.

Results

In this study, the patient with T2DM was older (54.53 vs. 48.36 years, P< 0.001), and had lower height (161.44 vs. 162.33 cm, P= 0.033), higher weight (76.18 vs. 73.77 kg, P< 0.001), higher BMI (29.24 vs. 28.02 kg/m2, P< 0.001), and lower MET (37.25 vs. 38.86 kcal/kg/day, P< 0.001) compared with the controls group (Table 1)(Fig. 1).

Regarding dietary intake of participants, the amount of energy (2381 vs. 2516 kcal, P< 0.001), total fat (61.47 vs. 64.99 g/day, P= 0.003), carbohydrate (393.16 vs. 415.9 g/day, P< 0.001), alcohol (0.025 vs. 0.035 g/day, P= 0.001), isoleucine (2.99 vs. 3.08 mg/day, P= 0.044) was significantly lower in cases than in controls. No difference was found between the intake of total protein, Leucine, and Valine in the two groups (Table 2).

As shown in Table 3, there was a significant negative association between the incidence of T2DM and the dietary levels of BCAA after adjustment for age and sex (OR = 0.972, CI 95%:0.948–0.996, P= 0.022) (Model 1). The result remained significant after additional adjustments for BMI and physical activity (OR = 0.967, CI 95%: 0.943– 0.992, P= 0.010) (Model 2). Interestingly, a positive association was found between T2DM and BCAAs after further adjustment for the calorie intake (OR = 1.7, CI 95%: 1.017– 1.119, P= 0.008).

Regarding the association between T2DM and different types of BCAAs, there was a negative association between T2DM and Isoleucine (OR = 0.892, CI 95%: 0.810–0.981, P= 0.019), Leucine (OR = 0.938, CI 95%: 0.887–0.991, P= 0.023), Valine (OR = 0.909, CI 95%: 0.837–0.987, P= 0.022) after adjustment for age and sex (Model 1). Also, there was a negative association between T2DM with Isoleucine (OR = 0.876, CI 95%: 0.795–0.966, P= 0.008) and Leucine (OR = 0.929, CI 95%: 0.878–0.983, P= 0.011) and Valine (OR = 0.937, CI 95%: 1.088–1.492, P= 0.094) after additional adjustments for BMI and physical activity (Model 2). The result remained significantly positive between T2DM and Isoleucine (OR = 1.248, CI 95%: 1.043–1.494, P= 0.016) Leucine (OR = 1.165, CI 95%: 1.046–1.299, P= 0.006) and Valine (OR = 1.274, CI 95%: 1.088–1.492, P= 0.003) after further adjustments for dietary calorie intake (Model 3).

Discussion

This case-control study for the first time, reports on the association between type 2 diabetes and dietary intake of BCAA. The results showed a significant positive association between T2DM and BCAA after calorie adjustment despite a negative association after adjustment for age, sex, and BMI. These findings

suggest that calorie intake may be a critical component in influencing the development of type 2 diabetes and insulin resistance. Additionally, participants'

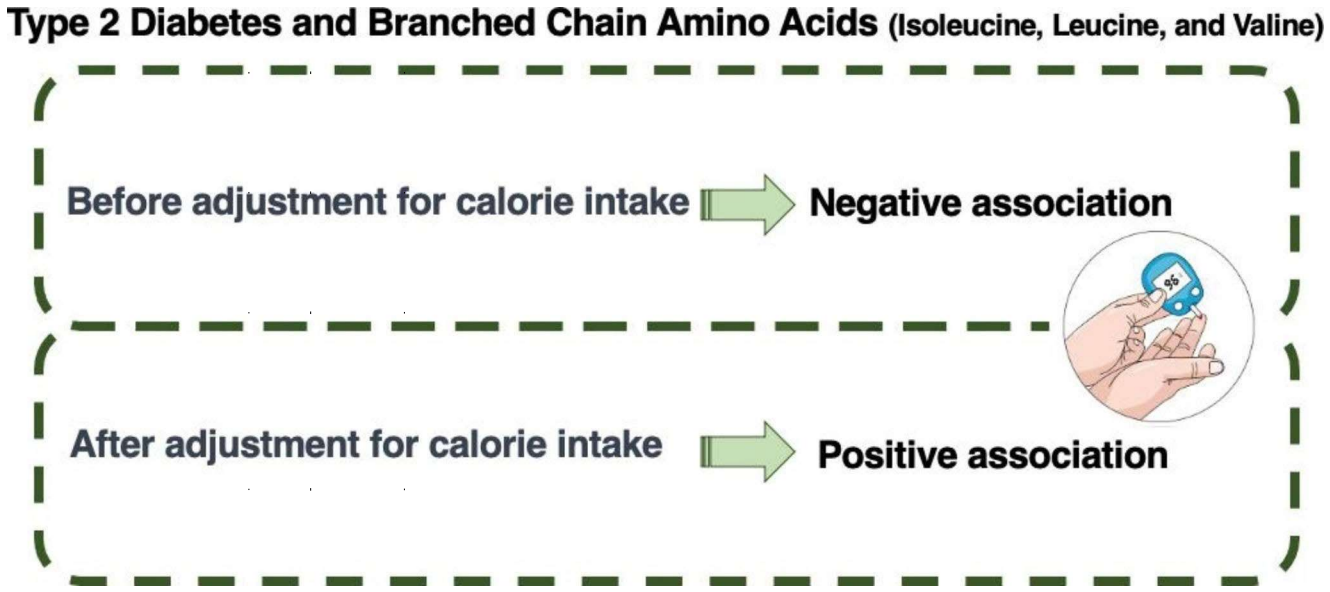

Fig. 1 The association between Type 2 Diabetes and Branched Chain Amino Acids (BCAA)

food consumption was substantially different between the cases and controls in terms of calories, total fat, carbohydrate, alcohol, and Isoleucine. Although there was no difference in the amounts of other dietary ingredients, including total protein, Leucine, or Valine between the two groups. This study after calorie adjustment had similar results to previous studies that type 2 diabetes can be associated with dietary intake of BCAA. A prospective cohort study [26] reported that intake of BCAA for the long-term could increase the risk of incident T2DM. These associations were independent of traditional risk factors of diabetes, like BMI. Another study showed that consumption of BCAA, Phenylalanine, and Tyrosine was associated with impaired fasting glucose and metabolic syndrome [27]. Results in a meta-analysis showed that elevation in the levels of BCAA could cause IR. In contrast, there is no association between elevated levels of Glutamine and Glycine and IR [28]. In fact, several studies, particularly in Caucasian and Asian ethnic groups, showed that high BCAA levels are associated with the development of type 2 diabetes [29–35]. In the Framingham Offspring study, elevated plasma BCAA levels had a positive correlation with fasting insulin levels that can predict the future risk of T2DM, especially in obese people [20]. Several studies also demonstrated an adverse association between BCAA and T2DM, because of BCAA's role in the development of IR [20, 36, 37]. In a Japanese study, BCAA was inversely associated with T2DM in women but were not significantly associated with T2DM in men [38]. These

differences could be in terms of the population age (35 years vs. 50–79 years) and T2DM ascertainment by self-report compared with HbA1c [7, 38]. Although another study reported that increased dietary intake of BCAA was associated with lower T2DM risk [38], ethnic differences can be responsible for such contradictory results.

The BCAA contributes to the development of T2DM via several mechanisms. BCAA can extend the secretion of glucagon and insulin secretion for a prolonged period [39]. Additionally, BCAA can play a major role in the pathophysiology of IR by promoting the production of hexosamine and gluconeogenic precursors [38]. Another hypothesis relates to the role of BCAA in activating the mechanistic target of the Rapamycin (mTORC) pathway. BCAA may activate mTORC1, with a negative effect on insulin receptors and promoting IR [40]. Amino acids can inhibit glucose transport and phosphorylation and impair glucose utilization and some studies showed that elevated levels of plasma amino acid can cause IR in skeletal muscle and stimulated endogenous glucose production in healthy men [40, 41]. Another mechanism is associated with changes in genes, especially the Protein Phosphatase, Mg^{2+}/Mn^{2+} Dependent 1 K (PPM1K), a gene encoding the mitochondrial phosphatase activating branched-chain keto acid dehydrogenase (BCKDH) complex, that has an important role in the development of T2DM [42].

This study reported an association between type 2 diabetes and dietary intake of BCAA. Using a validated FFQ to assess regular dietary intake to determine the consumption of dietary BCAA was an important strength. Thus, the cur- rent study has another important strength, including a larger sample size. Even though clinical measurements, not self- reports, were used to determine T2DM status. The primary drawback of the current investigation was the reliance on the patient's recollection of the self-reported FFQ, which was used to evaluate dietary consumption.

Conclusion

In this study, patients with T2DM were found to have lower levels of BCAAs in their diet compared to the control group, and there was a negative association between T2DM and the dietary levels of BCAAs. However, after adjustment for calorie intake, a positive association was found between T2DM and BCAAs. Furthermore, there was a negative association between T2DM and individual BCAAs (Isoleucine, Leucine, and Valine), but this association became positive after adjustment for dietary calorie intake. Further studies need to investigate the mechanisms behind these associations and whether BCAA supplementation could potentially benefit patients with T2DM. It would also be interesting to explore the role of other dietary factors in the development and progression of T2DM.

Acknowledgements The research was financially supported by Sabzevar University of Medical Sciences, Sabzevar, Iran.

Authors' contributions SAT, EB, ZA, GKH, SHT, SR, FA, ZS, AA, ZM and SD designed the study, involved in the data collection, analy- sis, and drafting of the manuscript. SD, SAM, SKH, BB, HSH, SN and MGH were involved in the design of the study, analysis of the data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding The research was funded by Sabzevar University of Medical Sciences, Sabzevar, Iran (Code 99220).

Data Availability Datasets used and/or analyzed during the current study are available from the corresponding author on reasonable requests.

Declarations

Ethics approval and consent to participate This study was approved by the Ethical Committee of the Research Ethics Committee of the Sabzevar University of Medical Sciences, Sabzevar, Iran. (code: IR.MEDSAB.REC.1400.040). All procedures of the studies involving human participants were by the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All participants signed informed consent forms. Informed consent was obtained from the adolescents and their parents to participate in the study.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

References

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81.

2. Sami W, Ansari T, Butt NS, Hamid MRA. Effect of diet on type 2 diabetes mellitus: a review. Int J Health Sci (Qassim). 2017;11(2):65–71.
3. Kaul N, Ali S, Genes. Genetics, and Environment in Type 2 diabetes: implication in Personalized Medicine. DNA Cell Biol. 2016;35(1):1–12.
4. Alhazmi A, Stojanovski E, McEvoy M, Garg ML. Macronutrient intake and type 2 diabetes risk in middle-aged australian women. Results from the australian Longitudinal Study on Women's Health. Public Health Nutr. 2014;17(7):1587–94.
5. Nuttall FQ, Almokayyad RM, Gannon MC. Comparison of a carbohydrate-free diet vs. fasting on plasma glucose, insulin and glucagon in type 2 diabetes. Metabolism. 2015;64(2):253–62.
6. Samkani A, Skytte MJ, Kandel D, Kjaer S, Astrup A, Deacon CF, et al. A carbohydrate-reduced high-protein diet acutely decreases postprandial and diurnal glucose excursions in type 2 diabetes patients. Br J Nutr. 2018;119(8):910–7.
7. van Nielen M, Feskens EJ, Mensink M, Sluijs I, Molina E, Amiano P, et al. Dietary protein intake and incidence of type 2 dia- betes in Europe: the EPIC-InterAct case-cohort study. Diabetes Care. 2014;37(7):1854–62.
8. Ericson U, Sonestedt E, Gullberg B, Hellstrand S, Hindy G, Wirfält E, et al. High intakes of protein and processed meat associate with increased incidence of type 2 diabetes. Br J Nutr. 2013;109(6):1143–53.
9. Tinker LF, Sarto GE, Howard BV, Huang Y, Neuhouser ML, Mossavar-Rahmani Y, et al. Biomarker-calibrated dietary energy and protein intake associations with diabetes risk among post- menopausal women from the Women's Health Initiative. Am J Clin Nutr. 2011;94(6):1600–6.
10. Malik VS, Li Y, Tobias DK, Pan A, Hu FB. Dietary protein intake and risk of type 2 diabetes in US Men and Women. Am J Epidemiol. 2016;183(8):715–28.
11. Bao W, Bowers K, Tobias DK, Hu FB, Zhang C. Prepregnancy dietary protein intake, major dietary protein sources, and the risk of gestational diabetes mellitus: a prospective cohort study. Diabetes Care. 2013;36(7):2001–8.
12. Yoon MS. The emerging role of branched-chain amino acids in insulin resistance and metabolism. Nutrients. 2016;8(7).
13. Lynch CJ, Adams SH. Branched-chain amino acids in meta- bolic signalling and insulin resistance. Nat Rev Endocrinol. 2014;10(12):723–36.
14. Ortega FB, Lavie CJ, Blair SN. Obesity and Cardiovascular Disease. Circ Res. 2016;118(11):1752–70.
15. Okekunle AP, Li Y, Liu L, Du S, Wu X, Chen Y, et al. Abnormal circulating amino acid profiles in multiple metabolic disorders. Diabetes Res Clin Pract. 2017;132:45–58.

16. Hu W, Sun L, Gong Y, Zhou Y, Yang P, Ye Z, et al. Relationship between branched-chain amino acids, metabolic syndrome, and Cardiovascular Risk Profile in a Chinese Population: a cross-sectional study. Int J Endocrinol. 2016;2016:8173905.
17. Flores-Guerrero JL, Osté MCJ, Kieneker LM, Gruppen EG, Wolak-Dinsmore J, Otvos JD et al. Plasma branched-chain amino acids and risk of Incident Type 2 diabetes: results from the PREVEND prospective cohort study. J Clin Med. 2018;7(12).
18. Lotta LA, Scott RA, Sharp SJ, Burgess S, Luan J, Tillin T, et al. Genetic predisposition to an impaired metabolism of the branched-chain amino acids and risk of type 2 diabetes: a mendelian randomisation analysis. PLoS Med. 2016;13(11):e1002179.
19. Ramzan I, Taylor M, Phillips B, Wilkinson D, Smith K, Hession K et al. A novel dietary intervention reduces circulatory branched- chain amino acids by 50%: a pilot study of relevance for obesity and diabetes. Nutrients. 2020;13(1).
20. Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, et al. Metabolite profiles and the risk of developing diabetes. Nat Med. 2011;17(4):448–53.
21. Layman DK. The role of leucine in weight loss diets and glucose homeostasis. J Nutr. 2003;133(1):261s–7s.
22. Adeva MM, Calviño J, Souto G, Donapetry C. Insulin resistance and the metabolism of branched-chain amino acids in humans. Amino Acids. 2012;43(1):171–81.
23. Zhang Y, Guo K, LeBlanc RE, Loh D, Schwartz GJ, Yu YH. Increasing dietary leucine intake reduces diet-induced obesity and improves glucose and cholesterol metabolism in mice via multimechanisms. Diabetes. 2007;56(6):1647–54.
24. Bloomgarden Z. Diabetes and branched-chain amino acids: what is the link? J Diabetes. 2018;10(5):350–2.
25. 2. Classification and diagnosis of diabetes: Standards of Medical
Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):15–s33.
26. Zheng Y, Li Y, Qi Q, Hruby A, Manson JE, Willett WC, et al. Cumulative consumption of branched-chain amino acids and incidence of type 2 diabetes. Int J Epidemiol. 2016;45(5):1482–92.
27. Weng L, Quinlivan E, Gong Y, Beitelshees AL, Shahin MH, Turner ST, et al. Association of branched and aromatic amino acids levels with metabolic syndrome and impaired fasting glucose in hypertensive patients. Metab Syndr Relat Disord. 2015;13(5):195–202.
28. Wang Q, Holmes MV, Davey Smith G, Ala-Korpela M. Genetic support for a causal role of insulin resistance on circulating branched-chain amino acids and inflammation. Diabetes Care. 2017;40(12):1779–86.
29. Klein MS, Shearer J. Metabolomics and type 2 diabetes: translating Basic Research into Clinical

Application. J Diabetes Res. 2016;2016:3898502.

30. Fiehn O, Garvey WT, Newman JW, Lok KH, Hoppel CL, Adams SH. Plasma metabolomic profiles reflective of glucose homeo- stasis in non-diabetic and type 2 diabetic obese african-american women. PLoS ONE. 2010;5(12):e15234.
31. Chen T, Ni Y, Ma X, Bao Y, Liu J, Huang F, et al. Branched-chain and aromatic amino acid profiles and diabetes risk in chinese populations. Sci Rep. 2016;6(1):1–8.
32. Guasch-Ferré M, Hruby A, Toledo E, Clish CB, Martínez- González MA, Salas-Salvadó J, et al. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. Diabetes Care. 2016;39(5):833–46.
33. Kujala UM, Peltonen M, Laine MK, Kaprio J, Heinonen OJ, Sundvall J, et al. Branched-chain amino acid levels are related with surrogates of disturbed lipid metabolism among older men. Front Med. 2016;3:57.
34. Yu D, Moore SC, Matthews CE, Xiang Y-B, Zhang X, Gao Y-T, et al. Plasma metabolomic profiles in association with type 2 diabetes risk and prevalence in chinese adults. Metabolomics. 2016;12(1):3.
35. Lee CC, Watkins SM, Lorenzo C, Wagenknecht LE, Il'yasova D, Chen Y-DI, et al. Branched-chain amino acids and insulin metabolism: the insulin resistance atherosclerosis study (IRAS). Diabetes Care. 2016;39(4):582–8.
36. Würtz P, Soininen P, Kangas AJ, Rönnemaa T, Lehtimäki T, Kähönen M, et al. Branched-chain and aromatic amino acids are predictors of insulin resistance in young adults. Diabetes Care. 2013;36(3):648–55.
37. Newgard CB. Interplay between lipids and branched-chain amino acids in development of insulin resistance. Cell Metabol. 2012;15(5):606–14.
38. Nagata C, Nakamura K, Wada K, Tsuji M, Tamai Y, Kawachi T. Branched-chain amino acid intake and the risk of diabetes in a japanese community: the Takayama study. Am J Epidemiol. 2013;178(8):1226–32.
39. Wada E, Kobayashi M, Kohno D, Kikuchi O, Suga T, Matsui S, et al. Disordered branched chain amino acid catabolism in pancreatic islets is associated with postprandial hypersecretion of glucagon in diabetic mice. J Nutr Biochem. 2021;97:108811.
40. Tremblay F, Lavigne C, Jacques H, Marette A. Role of dietary proteins and amino acids in the pathogenesis of insulin resistance. Annu Rev Nutr. 2007;27:293–310.
41. Krebs M, Krssak M, Bernroider E, Anderwald C, Brehm A, Meyerspeer M, et al. Mechanism of amino acid-induced skeletal mus- cle insulin resistance in humans. Diabetes. 2002;51(3):599–605.
42. Lotta LA, Scott RA, Sharp SJ, Burgess S, Luan Ja, Tillin T, et al. Genetic predisposition to an

impaired metabolism of the branched-chain amino acids and risk of type 2 diabetes: a mende- lian randomisation analysis. PLoS Med. 2016;13(11):e1002179.

Corresponding author

Saeid Doaei Doaei@gums.ac.ir

Table 1 Characteristics of the participants

	Controls (n = 3611)	Cases (n = 589)
Age (yrs)	48.36 ± 8.62	54.53 ± 7.75
Males (%)	1604 (44.42%)	267 (45.33%)
Females (%)	2007(55.58%)	322(54.67%)
Height (cm)	162.33 ± 9.18	161.44 ± 9.37
Weight (kg)	73.77 ± 13.41	76.18 ± 13.49
BMI (kg/m2)	28.02 ± 4.70	29.24 ± 4.74
MET (kcal/kg/day)	38.86 ± 7.91	37.25 ± 6.86

Abbreviations: BMI: Body Mass Index; Met: Metabolic Equivalent Task

Quantitative and qualitative data are presented as mean ± SD and number (%), respectively

*The analyses were performed using the independent T-test for quantitative variables and a chi

Table 2 Average daily dietary intake of the participants

	Controls	Cases	P*
Energy (Kcal)	2516 ± 78	2381 ± 80	< 0.001
Protein (g/day)	78.99 ± 26.06	76.60 ± 25.97	0.400
Total fat (g/day)	64.99 ± 25.13	61.47 ± 26.28	0.003
Carbohydrate (g/day)	415.9 ± 137.51	393.16 ± 140.01	< 0.001
Alcohol (g/day)	0.035 ± 0.079	0.025 ± 0.061	0.001
Isoleucine (mg/day)	3.08 ± 1.02	2.99 ± 1.04	0.044
Leucine (mg/day)	5.29 ± 1.76	5.13 ± 1.80	0.053
Valine (g/day)	3.63 ± 1.19	3.52 ± 1.22	0.051
BCAAs (g/d)	12.01 ± 3.98	11.65 ± 4.08	0.046

Data are presented as mean ± SD.

*The analyses were performed using the independent T-test