MLS - HEALTH & NUTRITION RESEARCH

https://www.mlsjournals.com/MLS-Health-Nutrition

Health & Nutrition Research

Como citar este artículo:

Pérez-Lagos, F. J. (2022). Efecto dual de los aminoácidos de cadena ramificada y su relación con la resistencia a la insulina. *MLS Health & Nutrition Research, 1*(1), 23-41.

DUAL EFFECT OF BRANCHED-CHAIN AMINOACIDS AND THEIR RELATIONSHIP WITH INSULIN RESISTANCE

Fernando Josué Pérez Lagos
Universidad Europea del Atlántico, UNINI
perezlagosf@gmail.com · https://orcid.org/0000-0003-2659-2238

Abstract. Insulin resistance is a complication present in subjects with obesity and has been identified as a key factor in the appearance and progression of diabetes mellitus. Numerous studies highlight the benefits of a high-protein diet for both the treatment of obesity and insulin resistance. However, despite these benefits, a high protein diet has been linked to worse metabolic dysfunction, and even worsened insulin resistance. Thanks to studies in metabolomics, it has been postulated that branched-chain amino acids may be mediating these contradictory effects of a high protein intake and its relationship with insulin resistance. This narrative review compiles emerging evidence regarding the paradoxical effect that branched-chain amino acids can have on body homeostasis. Different contexts such as the presence of obesity, dietary patterns, origin of proteins that contain branched-chain amino acids, physical exercise, intestinal microbiota, sex as well as genetic load, are variables to take into account to evaluate the role of these amino acids.

Keywords: BCAA, branched-chain amino acids, insulin resistance, obesity, diabetes mellitus.

EFECTO DUAL DE LOS AMINOACIDOS DE CADENA RAMIFICADA Y SU RELACION CON LA RESISTENCIA A LA INSULINA

Resumen. La resistencia a la insulina es una complicación presente en sujetos con obesidad y se ha identificado como un factor clave en la aparición y progresión de la diabetes mellitus. Numerosos estudios resaltan los beneficios de una dieta con alto contenido de proteínas tanto para el tratamiento de la obesidad como para la resistencia a la insulina. No obstante, a pesar de dichos beneficios, una dieta hiperproteica se ha relacionado con una peor disfunción metabólica, e incluso empeorando la resistencia a la insulina. Gracias a estudios en metabolómica se ha postulado que los aminoácidos de cadena ramificada pueden estar mediando estos efectos contradictorios de una alta ingesta de proteínas y su relación con la resistencia a la insulina. En la presente revisión narrativa se recopila la evidencia emergente en cuanto al efecto paradójico que pueden desempeñar los aminoácidos de cadena ramificada en la homeostasis del organismo. Diferentes contextos como la presencia de obesidad, patrones dietéticos, origen de proteínas que contengan aminoácidos de cadena ramificada, ejercicio físico, microbiota intestinal, sexo, así como la carga genética, son variables a tener en cuenta para evaluar el rol de estos aminoácidos.

Palabras clave: BCAA, aminoácidos de cadena ramificada, resistencia a la insulina, obesidad, diabetes mellitus.

Introduction

Insulin resistance (IR) is a common characteristic that can present pathologies such as obesity and type 2 diabetes mellitus (DM2); in addition to atherosclerosis, dyslipidemia, and hypertension, which are commonly included in the metabolic syndrome, which has a great impact on the mortality and morbidity of individuals (1) (2). In order to alleviate this situation, it is common to perform dietary-nutritional interventions with a modification of macronutrients, usually by increasing the number of proteins and decreasing carbohydrates or fats. All this with the aim of reducing the fat percentage and consequently improving other parameters such as IR (3).

Proteins are one of the three macromolecules present in food. Due to their great structural diversity, they are capable of performing a large number of crucial functions in the homeostasis of the human organism such as body composition, food intake, satiety, protein synthesis, among others (4) (5). In the short term, diets with a high protein intake can influence weight control; in addition, thanks to their insulinotropic effect, they can help glycemic control (6) (7). However, paradoxically, different studies have related a high dietary protein intake with poorer metabolic health (8). Similarly, in some long-term investigations, a greater association has been found between a diet rich in protein and the risk of insulin resistance (9) (10).

For some time now, the results of various investigations have pointed to the structural units of proteins as possible mediating agents of this association and, specifically, to the branched-chain amino acids (BCAA) (11) (12). BCAAs comprise leucine, isoleucine, and valine, which are essential amino acids, which implies that the organism can only obtain them through food or through muscle catabolism. In comparison with other essential amino acids, BCAAs are found in greater proportion in dietary proteins, ranging from 17% to 30% in some food groups, with some dairy products such as cheese (30.41%), fish and seafood (17.57%), red meat and poultry (29.73%) having the highest content (13). Potential beneficial effects of BCAAs on adiposity and metabolic syndrome have been reported (14). These results have been supported by mechanistic research in rats where it has been reported that BCAAs improve glucose uptake in muscles (15).

Despite the potential benefits of BCAAs, in recent years, metabolomic studies have shown a significant relationship between high circulating levels of BCAAs and insulin resistance. It is noteworthy that obese subjects presented a higher level of 20% and 14% for valine and leucine/isoleucine, respectively, compared to lean subjects (16).

The aim of this narrative review is to describe the dual effect that, depending on the context, branched-chain amino acids can have on human health. It will also describe the different specific aspects that can modulate the role of these amino acids.

Method

A search for articles was conducted during the period February to May 2020 with a subsequent update from December 1 to December 10, 2021. All articles reviewed were in English. The PubMed database as the main source and Google Scholar as a complementary source. Articles were included where the potential beneficial as well as detrimental effects of high consumption of branched-chain amino acids on health were analyzed, with a special emphasis on their relationship with insulin resistance. Boolean operators such as AND were used to narrow the results. The reference list of these as well as the list of recommended "related articles" in PubMed were consulted. Some search terms used were "excessive consumption AND branched-chain amino acids," "insulin resistance AND branched-chain amino acids," "obesity AND branched-chain amino acids." A total of 85 original articles were obtained, of which 14 articles were used to discuss their results. The characteristics taken into account for the selection of the latter 14 articles were that the interventions were in humans, original articles no more than 10 years old, quantification of branched-chain amino acids either by plasma analysis or dietary intake to analyze their impact after the experiment.

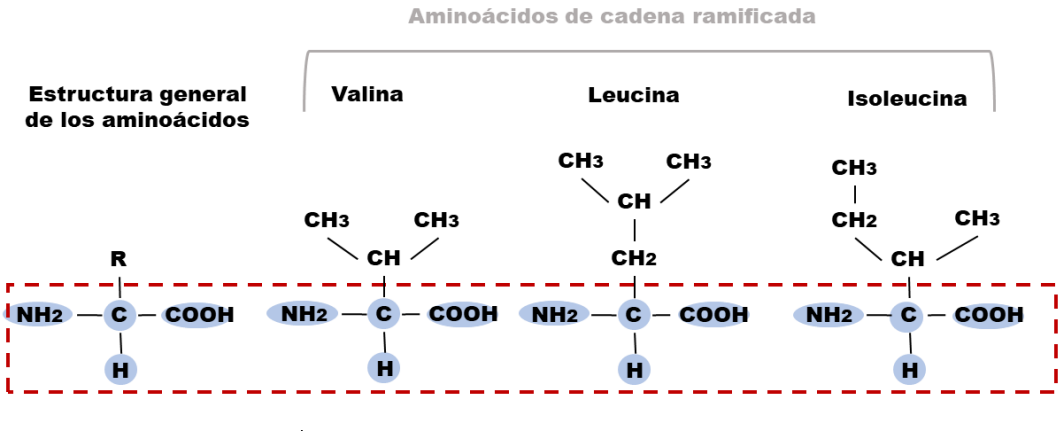
Results

A search for articles was conducted during the period February to May 2020 with a subsequent update from December 1 to December 10, 2021. All articles reviewed were in English.

Digestion, absorption, and catabolism of branched-chain amino acids

Proteins, after being ingested in the diet, are broken down in the gastrointestinal system. First, digestion begins in the stomach mediated by pepsins, and it then continues in the small intestine with the help of pancreatic proteases released by the exocrine pancreas. As a result of these processes, the proteins are transformed into amino acids and smaller oligopeptides. Finally, brush border peptidases finish digesting the oligopeptides into free amino acids, dipeptides, and tripeptides, which are taken to the enterocyte where they undergo further digestion. BCAAs, unlike other essential amino acids, differ in having aliphatic side chains with a branch point as shown in Figure 1.

Figure 1. Chemical structure of BCAAs. The dotted rectangle indicates the basic structure of all amino acids. Generic BCAAs have an aliphatic side chain with a branching point. [Source: Own elaboration]

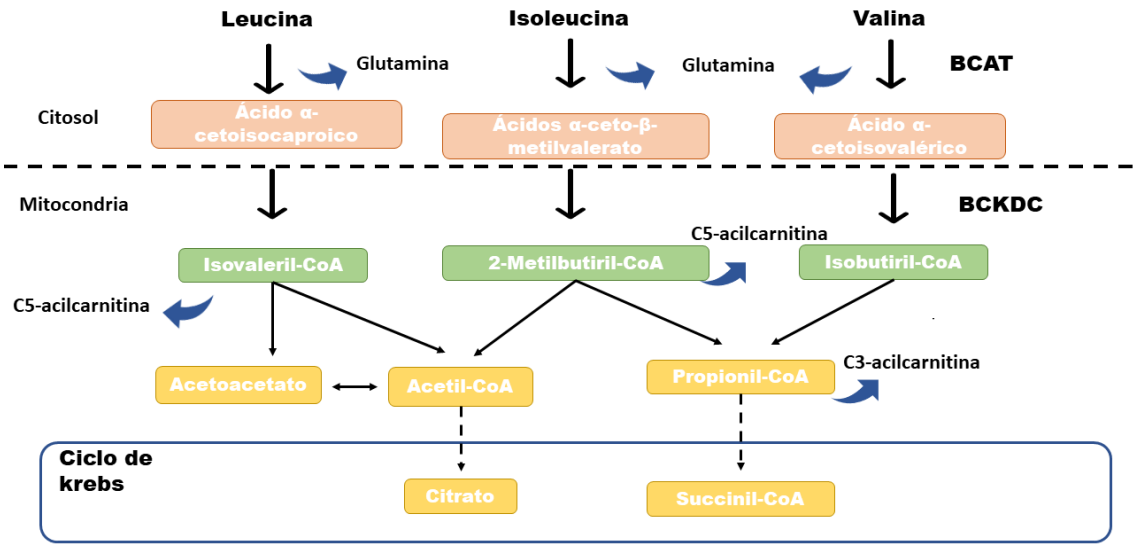


In blood plasma, after a meal rich in BCAAs, these amino acids increase approximately 2 to 3 times and then decrease to their initial value after approximately 3 hours. Furthermore, it should be noted that the kinetics of their absorption will differ according to the source of protein ingested (17) (18). After absorption, BCAAs are not taken to the liver to be metabolized as is the case with other amino acids. About 80% of BCAAs are transported to the blood circulation to be directly absorbed by peripheral tissues, such as skeletal muscle and adipose tissue, where they are directly metabolized (8).

Already in the extrahepatic tissues (mainly muscle and adipose tissue), BCAAs can undergo further catabolism. In their first reactions BCAAs are metabolized simultaneously. First, BCAAs undergo reversible transamination by branched-chain amino acid aminotransferases (BCATs), which convert them to branched-chain alpha-ketoacids (BCKAs), alpha-ketoisocaproate, alpha-ketoisovalerate, and alpha-keto-beta-methylvaleric for leucine, valine, and isoleucine, respectively. BCKAs can be released into the bloodstream and absorbed by other tissues; however, the normal pathway they take is to continue to the next step in their catabolism, which involves irreversible oxidative decarboxylation, mediated by the branched-chain keto acid dehydrogenase complex (BCKDC) located on the mitochondrial surface. It is noteworthy that BCKDCs have a higher activity in the liver and lower activity in muscle, adipose tissues, and brain (20). This fact is of great relevance since, as will be discussed later, the defects in BCAA catabolism in extrahepatic tissues have been postulated as a potential pathway for the development of insulin resistance.

Finally, oxidized alpha-keto acids diverge into alternate metabolic pathways to produce branched-chain acyl-CoA esters: acetyl-CoA and Succinyl-CoA for leucine, valine, and isoleucine, respectively, as depicted in Figure 2 (21) (22).

Figure 2. Catabolism of branched-chain amino acids. BCAAs undergo a first reaction in the cytosol mediated by BCAT producing α-ketoacids. Next, the keto acids undergo an irreversible oxidative decarboxylation by BCKDC at the mitochondrial membrane. Finally, BCAAs can be incorporated into the Krebs cycle for energy production. Depending on the context, BCAAs can produce glutamine or acylcarnitines, the latter of which are related to the genesis of IR. [Source: Image adapted from: Holeček M. Nutr Metab (Lond). 2018 May 3;15:33. (23)]



Actions of branched-chain amino acids on the health of the body

Undoubtedly, due to their characteristics, BCAAs play very relevant roles in the homeostasis of the organism. Therefore, it is important to maintain a correct balance of these amino acids.

BCAAs are of particular relevance in health due to their close relationship with important metabolic pathways. Among these, protein synthesis is one of the most recognized functions performed by proteinogenic amino acids, including BCAAs. Which is of particular importance for muscle proteins that are in constant protein turnover. BCAAs induce an anabolic state as long as there is a good availability of all essential amino acids for muscle protein synthesis; representing up to 35% of essential amino acids present in muscle (24) (25). This has been studied especially during training to achieve a greater synthesis of muscle proteins during exercise (26). Furthermore, because of their ability to be incorporated into the Krebs cycle, BCAAs are involved in energy production where, through their catabolites, they can act as metabolic substrates (23).

Likewise, in recent years it has been demonstrated the important role that BCAAs can have in different aspects of health such as the functioning of the gastrointestinal tract, blastocyst development, fetal growth, immune function, among others, which indicates the important role that BCAAs play in the homeostasis of the organism (27).

Reduced branched-chain amino acid balance

The extrahepatic tissues, as well as the enzymes involved in the processing of BCAAs, play an important role in maintaining the levels of these amino acids at optimal levels. However, in certain situations where these variants are put out of balance, a marked role is observed in the clinical manifestations of various diseases. An excess of BCAAs has been related to important metabolic disorders, while in other scenarios their contribution is crucial to improve the prognosis of serious pathologies. Therefore, it is necessary to know the specific context of

health or disease in order to determine the different variables where BCAAs can play a dual role.

Several studies highlight the therapeutic effects that BCAAs can have in different conditions characterized by a basic catabolic state, where the concentrations of these amino acids are diminished. Such is the case of liver cirrhosis (LC), which is characterized by alterations in the structure and function of the liver (28). In this pathology there is a marked decrease in plasma BCAA concentration that may be caused by reduced food intake, hypercatabolism, and ammonia detoxification in skeletal muscle. Because some tissues are able to utilize BCKAs to produce the amino acid glycine. This reduces ammonia accumulation and, consequently, the concentration of BCAA (29). Although there are divergences in clinical studies on the use of BCAA in LC, supplementation with these amino acids when their requirements are not reached in the diet results in a greater regulation of ascites, cachexia, hepatic encephalopathy, and even insulin resistance (30) (31) (32) (33).

Similarly, other diseases that present low urea and high ammonia levels in the blood, such as urea cycle disorders, result from the detoxification of ammonia in the liver. In these disorders it is common to find an increase in the amino acid glycine, as well as a decrease in BCAA levels, especially when acute metabolic decompensation occurs. These alterations support the important role that BCAAs may play in homeostasis (34) (35). Similarly low levels of both BCAAs and α-keto acids have been reported in blood plasma and skeletal muscle in patients with untreated chronic renal failure, and during dialysis (36). The metabolic acidosis present in CKD, together with hemodialysis, represent the main factor for the depletion of proteins in general and specifically of BCAA and their catabolites (37). The normalization of BCAA together with α-ketoacids in plasma, through oral supplementation, was associated with an improvement in appetite and nutritional status (38) (39).

High branched-chain amino acid balance

Elevated BCAA levels and their negative role in health are evidenced by inborn errors of BCAA metabolism such as maple syrup urine disease (MSUD). In this pathology, alterations in BCAA catabolism occur, affecting the action of BCKDCs, thus causing a marked elevation of both BCAAs and their catabolites in urine, blood, and tissues. These higher levels are toxic to the brain and lead to irreversible neurological complications or even death for patients. In animal models with MSUD, it has been shown that BCAA administration can cause hippocampal DNA damage (40). Therefore, the exhaustive control of BCAAs in the diet is essential to improve the clinical and prognostic outcome of this disease (41).

On the other hand, abnormally elevated BCAA levels have been reported in obese subjects since the 1960s (42). Subsequent metabolomic studies have correlated these elevated BCAA levels with the risk of insulin resistance and future type 2 diabetes mellitus (43) (16). These results were confirmed by animal studies where administration of BCAAs together with a high-fat diet resulted in increased insulin resistance (16). The above conclusions are in line with another study which concluded that a BCAA-restricted diet improved insulin sensitivity in skeletal muscle of rats (44).

Additionally, in another study, this time in humans, a decrease in plasma BCAA was found in obese subjects when they underwent weight loss surgery. These changes were paralleled by an increase in mitochondrial BCAT and BCKD in omental and subcutaneous fat (45). Another study described a reduction of BCAA and acylcarnitines after weight reduction

in obese adolescents, resulting in improved insulin sensitivity (46). In addition, after an overnight fast, high levels of BCAA are still observed (47).

These results seem to point to excess adiposity as a potential mediator in the detrimental effects of BCAAs. Obesity, along with chronic excessive dietary energy intake, are the main predisposing factors for the development of IR (48) (49). Although there are multiple factors that contribute to the development of obesity, it is well known that energy intake in excess of expenditure is a major contributor to its development. Likewise, obesity triggers inflammation that affects multiple organs crucial in insulin action and glucose regulation (such as skeletal muscle, adipose tissue, and liver) and in the development of IR (50). The accumulation of excessive energy in the form of fat causes mechanical stress on the adipose cell, resulting in chronic low-grade inflammation caused by activation of the innate immune system (51) (52).

Apart from adipose tissue, this inflammation is also present in other peripheral tissues. The liver may also experience activation of inflammatory pathways during obesity, as macrophages increase along with local production of chemokines and inflammatory cytokines that may predispose to IR in hepatocytes (53) (54). For their part, myocytes in skeletal muscle are another cell type that is associated with increased obesity-related inflammation through the infiltration of immune cells that may contribute to IR locally in this tissue (55).

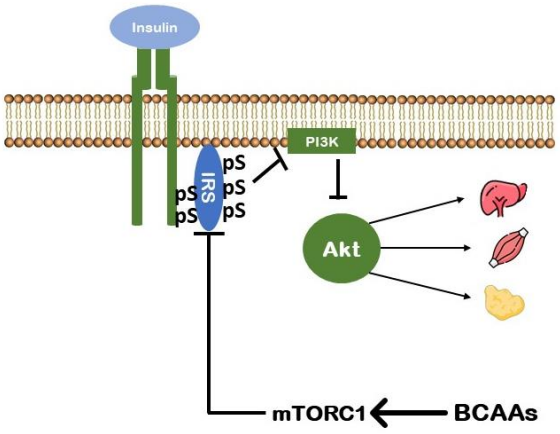
Branched-chain amino acids and their relationship to insulin resistance

In some research, like BCAAs, other amino acids have been associated with an increased risk of IR. However, in the case of BCAAs, there are mechanisms described by which increased BCAAs may contribute to future metabolic problems such as IR. Therefore, further understanding of the pathways that may be mediating between BCAAs and the development of IR is needed.

Mammalian target of rapamycin pathway

The mTOR complex is a serine/threonine of the PI3K-related kinase family. The mTOR pathway is the main pathway capable of coordinating local nutrients for cell growth and proliferation. The mTOR is the component of two multiprotein complexes known as mTORC1 and mTORC2 (56). The function of mTORC1 is to maintain a balance between anabolism and catabolism in response to various stimuli, including the concentration of BCAA. BCAAs, through the Rag family of GTPases, can act as a nutrient signal and activate the mTORC1 pathway at the lysosomal surface (57). Chronic activation of mTORC1 causes negative feedback leading to serine phosphorylation of the insulin receptor substrate (IRS), which impacts on Akt and consequently leading to IR in different tissues such as skeletal muscle, liver, and adipose tissue (58).

Figure 3. Proposed mechanism by which branched-chain amino acids contribute to insulin resistance through activation of mTORC1**.** After insulin binding to the α-subunit of the insulin receptor, it recruits IRS which triggers a signaling cascade activating the phosphatidylinositol-3-kinase (PI3K)/Akt pathway responsible for most of the metabolic actions of insulin in tissues such as liver, skeletal muscle, and adipose tissue. BCAAs, through chronic stimulation of mTORC1, are able to phosphorylate different IRS serines, resulting in decreased insulin actions such as glucose uptake and glucose synthesis in tissues crucial in their metabolism. [Source: Image adapted from: Yoon MS. Nutrients. 2016 Jul 1;8(7):405. (59)]



Altered branched-chain amino acid catabolism in peripheral tissues

The catabolism of BCAAs in the different peripheral tissues such as skeletal muscle, adipose tissue, and liver is well regulated to maintain a correct negative and positive balance of BCAAs. Interestingly, these same tissues are key organs in the metabolization of glucose and in the normalization of fasting and postprandial plasma insulin levels. Impairment of BCAA catabolism would occur in a manner similar to a domino effect, with excess fat being a major catalyst. Obesity through various pathways, including inflammation, could impair catabolic pathways in tissues, including adipose, leading to an overload on other tissues as discussed below.

Excess fat in adipose tissue, by mechanisms yet to be further explored, may exert an influence on genes encoding key enzymes in BCAA metabolism such as BCAT and BCKDH, leading their enzymes to decrease their transcription and activity (45). This is supported by studies where down-regulation of BCAA enzyme mRNA was seen to be caused by selective overexpression in adipose tissue of Glut4 in animals with an obese phenotype (60).

In several investigations in transgenic rats with alterations in mitochondrial BCAT, as well as in BCKD, cause sustained changes in plasma BCAA concentrations (61) (62) Therefore, the reduction of these enzymes may have an impact on BCAA catabolism in this tissue causing other tissues such as muscle and liver to have to break down a greater amount of BCAA.

By increasing BCAA catabolism in the ME, an intermediate in valine catabolism, 3-hydroxy-isobutyrate (3-HIB) is formed. 3-HIB regulates transendothelial transport as well as uptake of free fatty acids from plasma into muscle cells. This leads to an elevated accumulation of lipid oxidation products within muscle fibers such as diacylglycerides and ceramides triggering insulin resistance in this tissue (63).

In skeletal muscle, the expression of BCKDH is very low, which hinders the complete breakdown of the BCKA previously generated. Therefore, BCKA are transported to the liver since this organ has a higher expression of BCKDH compared to skeletal muscle (64). They can then be broken down to produce acyl-CoA and propionyl-CoA, which are then introduced into the Krebs cycle for oxidation. However, if the production of acyl-CoA and propionyl-CoA exceeds the oxidative capacity of the mitochondria, acylcarnitines can be produced, impairing mitochondrial CAT. Consequently, the liver's ability to oxidize fatty acids and glucose is reduced causing these products to accumulate excessively, altering insulin, signaling and causing hepatic IR.

In addition, the production of acetyl-CoA is able to increase gluconeogenesis and lipogenesis, which added to the oxidative stress of mitochondria, further promotes IR in this organ (65). Although mechanistic studies in rats supplemented with BCAA have highlighted positive effects such as improved glucose tolerance, decreased inflammation in adipose tissue, and improved insulin signaling in adipose tissue in insulin-resistant db/db mice.

In primates, including humans, BCAA metabolism is less active in the liver than in rats (66) (67). This is because the activity of catabolic enzymes is much higher in rats than in primates, so the capacity to eliminate branched-chain alpha-ketoacids is much higher. Specifically, 83%, 3%, and 1% of BCKDs in rats are expressed in liver, skeletal muscle, and brain, respectively. Whereas in primates, 13%, 54%, and 20% are expressed in liver, muscle, and brain, respectively. Therefore, the best models for testing BCAA overdoses would be in nonhuman primates (68).

Other aspects to take into account

High BCAA levels as a consequence of IR

The question remains as to whether the consumption of foods rich in BCAA is capable of increasing IR; or, on the contrary, the increase in BCAA is a subsequent consequence of IR. Since the antiproteolytic action of insulin is altered and as a consequence protein catabolism increases secondary to IR (69). However, in the study conducted by Asghari et al. (70), it was described that a high BCAA intake is related to an increased risk of IR in overweight adults followed for 2.3 years. Another study by Zhen et al. (71) prospectively analyzed the association between long-term BCAA intake and DM2 incidence. The population consisted of normal-weight and overweight Americans. The study showed a strong correlation of BCAA intake with an increased risk of DM2. Notably, total BCAA intake was positively associated with BMI and protein intake. However, it was not clearly distinguished whether these effects were mediated by BCAA, total protein, or animal protein. In contrast to the above results, in the trial conducted by Woo et al. (72), where they selected 12 heterogeneous individuals between 20 and 60 years of age, obese and prediabetic, no significant differences were observed for body weight, fat mass, muscle mass, BMI, fasting plasma glucose and insulin, and HOMA-IR after BCAA supplementation for 4 weeks. In addition, BCAA consumption did not cause an increase in plasma BCAA. However, as the authors point out, BCAA concentrations could have been affected by the gut microbiome, as gut bacteria are capable of synthesizing fatty acids from AA including BCAA (73). Additionally, the final results of the study by Nagata et al. (74) suggest that high intakes of BCAAs were associated with a decreased risk of diabetes in women. While in men, total BCAA intake was not significantly associated with diabetes risk after controlling for covariates. In addition, higher leucine intake was significantly associated with a decreased risk of diabetes. Interestingly, in another study (75), after analyzing more than 8000 Chinese individuals predisposed to have DM2 with normal weight and overweight, it was found that higher BCAA intake and DM2 risk depended on the context of dietary patterns and not only on BCAA intake.

Modification of BCAA concentrations by diet

Another important factor is whether the amounts of BCAA in the diet will have an impact on plasma concentrations. Some studies have addressed this question such as the one conducted by Karusheva et al. (76), where they investigated whether lower BCAA intake improved short-term insulin sensitivity in overweight and obese subjects aged 40 to 60 years.

The sources of BCAA were both foods available from grocery stores and markets as amino acid supplements. After the intervention, it was found that the basal plasma BCAA level went from 507±90 to 422±56 µmol/L, representing a decrease of 17%. In addition, we found a decrease in insulin secretion; increased postprandial insulin sensitivity; increased stimulation of mitochondrial efficiency in adipose tissue and, finally, we found alterations in the composition of the intestinal microbiome in favor of bacteroidetes.

Another study with a larger sample size concluded that BCAA concentrations are directly related to the risk of DM2. High BCAA concentrations were positively related to the consumption of legumes and red meat. In addition, it was shown that basal BCAA concentrations were significantly higher in men than in women. Also, BCAA levels decreased in participants receiving the intervention (411±113 to 363±80.5 nmol/nL), and the improvement in BCAA concentration occurred independently of weight loss, although there was a greater decrease in subjects with greater weight loss (77).

Similar results were obtained by Ruiz Canela and collaborators (78), who investigated the association of one-year changes in BCAA and aromatic amino acids (AAA) in 892 patients with type 2 diabetes, overweight, or slightly obese within the PREDIMED trial. It was concluded that the Mediterranean diet + extra virgin olive oil intervention was associated with significant reductions in BCAA after one year.

In contrast to these results, another study evaluated that a specific short-term dietary intervention modestly modified fasting BCAA levels in healthy individuals. The researchers used diets low in BCAAs, using plant foods and supplements free of these amino acids; on the other hand, in the high BCAA diet, they used foods such as meat and supplements high in BCAAs. However, the authors point out that it is possible that dietary manipulation of BCAA may be more effective in obese people or those with insulin resistance who are known to have dysregulation of BCAA metabolism (79).

Recently, an isocaloric dietary intervention with BCAA restriction (-50%) was performed on 12 healthy individuals for 7 days. For this purpose, the participants followed diets low in BCAA while consuming a BCAA-free supplement. At the end of the study, the initial plasma BCAA value was significantly reduced from 437±60 to 217±40 µmol/L. Similarly, there was an improvement in insulin resistance. It is worth mentioning that the low number of subjects and the short intervention are important factors to take into account for the interpretation of their results (80).

Genetic variability

Genome-wide association studies (GWAS) are showing results on how the genetic variability of each individual plays a key role in the changes and effects of plasma BCAAs. Specifically, it has been described that some polymorphisms such as rs1440581 may be related to insulin resistance (81). In this line, it has been described that increased BCAA intake is associated with an increased predisposition to DM2 when the genetic predisposition was high (82). Similarly, these amino acids were found to be able to increase the risk of both DM2 and glycosylated hemoglobin in incident diabetes patients with high genetic susceptibility for altered BCAA metabolism (83).

Physical exercise

Physical exercise can be another very potent factor in mediating the effects that BCAAs and their catabolites can trigger in the body. Physical exercise is able to act on the ME and affect the major organ in the regulation of BCAA catabolism. Although more research is needed, some actions such as improving the oxidative potential of mitochondria may lead to increased elimination of BCAA intermediates, in turn, improving IR (84). Similarly, it has been described that physical exercise triggers mechanisms for more efficient elimination of BCAA- and acylcarnitine-derived catabolites in the ME via glycine conjugation in the liver in obese individuals (85).

Conclusion

Emerging evidence points to the great relevance that a high intake of dietary BCAAs can play in the health of people particularly with metabolic disorders such as insulin resistance. High plasma levels of branched-chain amino acids lead to a worsening of metabolic health, while their limited intake has an impact on the improvement of some parameters such as blood glucose homeostasis. It is important to emphasize that these effects become noticeable in people who present a basic alteration, as is the case of excess adiposity. Therefore, a dietary pattern that not only quantifies the proportions of macronutrients but also the quality and quantity of their functional units. In this case, branched-chain amino acids could be a therapy to be considered to combat the complications associated with obesity such as insulin resistance. Future studies should take into account variables such as physical exercise, genetic load, as well as gut microbiota, sex, and dietary patterns in both the quality and type of protein and other accompanying dietary components such as fats.

References

(1) Garber AJ. Obesity and type 2 diabetes: which patients are at risk? Diabetes Obes Metab. 2012 May;14(5):399-408. Disponible en: http://dx.doi.org/10.1111/j.1463-1326.2011.01536.x

(2) Reaven GM. Insulin resistance/compensatory hyperinsulinemia, essential hypertension, and cardiovascular disease. J Clin Endocrinol Metab. 2003 Jun;88(6):2399-403. Disponible en: http://dx.doi.org/10.1210/jc.2003-030087

(3) Hansen TT, Astrup A, Sjödin A. Are Dietary Proteins the Key to Successful Body Weight Management? A Systematic Review and Meta-Analysis of Studies Assessing Body Weight Outcomes after Interventions with Increased Dietary Protein. Nutrients. 2021 Sep 14;13(9):3193. Disponible en: http://dx.doi.org/10.3390/nu13093193

(4) Gil Á. Tratado de nutrición. Tomo 1. Bases fisiológicas y bioquímicas de la nutrición. Medicina contreras (ed.). Madrid: Acción Medica; 2005

(5) Greco E, Winquist A, Lee, T. J., Collins, S., Lebovic, Z., Zerbe-Kessinger, T, et al. The role of source of protein in regulation of food intake, satiety, body weight and body composition. J. Nutr. Health Food Eng. 2017;6(6):186-193. Disponible en: http://dx.doi.org/10.15406/jnhfe.2017.06.00223

(6) Huang G, Pencina K, Li Z, Apovian CM, Travison TG, Storer TW, et al. Effect of Protein Intake on Visceral Abdominal Fat and Metabolic Biomarkers in Older Men With Functional Limitations: Results From a Randomized Clinical Trial. J Gerontol A Biol Sci Med Sci. 2021 May 22;76(6):1084-1089. Disponible en: http://dx.doi.org/10.1093/gerona/glab007

(7) El Khoury D, Hwalla N. Metabolic and appetite hormone responses of hyperinsulinemic normoglycemic males to meals with varied macronutrient compositions. Ann Nutr Metab. 2010;57(1):59-67. Disponible en: http://dx.doi.org/10.1159/000317343

(8) Rietman A, Schwarz J, Tomé D, Kok FJ, Mensink M. High dietary protein intake, reducing or eliciting insulin resistance? Eur J Clin Nutr. 2014 Sep;68(9):973-9. Disponible en: http://dx.doi.org/10.1038/ejcn.2014.123

(9) Ricci G, Canducci E, Pasini V, Rossi A, Bersani G, Ricci E, et al. Nutrient intake in Italian obese patients: relationships with insulin resistance and markers of non-alcoholic fatty liver disease. Nutrition. 2011 Jun;27(6):672-6. Disponible en: http://dx.doi.org/10.1016/j.nut.2010.07.014

(10) Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. Diabetes Care. 2010 Jan;33(1):43-8. Disponible en: http://dx.doi.org/10.2337/dc09-1321

(11) Layman DK, Baum JI. Dietary protein impact on glycemic control during weight loss. J Nutr. 2004 Apr;134(4):968S-73S. Disponible en: http://dx.doi.org/10.1093/jn/134.4.968S

(12) Nair KS, Short KR. Hormonal and signaling role of branched-chain amino acids. J Nutr. 2005 Jun;135(6 Suppl):1547S-52S. Disponible en: http://dx.doi.org/10.1093/jn/135.6.1547S

(13) Haydar S, Paillot T, Fagot C, Cogne Y, Fountas A, Tutuncu Y, et al. Branched-Chain Amino Acid Database Integrated in MEDIPAD Software as a Tool for Nutritional Investigation of Mediterranean Populations. Nutrients. 2018 Oct 1;10(10):1392. Disponible en: http://dx.doi.org/10.3390/nu10101392

(14) Layman DK, Walker DA. Potential importance of leucine in treatment of obesity and the metabolic syndrome. J Nutr. 2006 Jan;136(1 Suppl):319S-23S. Disponible en: http://dx.doi.org/10.1093/jn/136.1.319S

(15) Doi M, Yamaoka I, Nakayama M, Sugahara K, Yoshizawa F. Hypoglycemic effect of isoleucine involves increased muscle glucose uptake and whole body glucose oxidation and decreased hepatic gluconeogenesis. Am J Physiol Endocrinol Metab. 2007 Jun;292(6):E1683-93. Disponible en: http://dx.doi.org/10.1152/ajpendo.00609.2006

(16) Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009 Apr;9(4):311-26. Disponible en: http://dx.doi.org/10.1016/j.cmet.2009.02.002

(17) Boirie Y, Dangin M, Gachon P, Vasson MP, Maubois JL, Beaufrère B. Slow and fast dietary proteins differently modulate postprandial protein accretion. Proc Natl Acad Sci U S A. 1997 Dec 23;94(26):14930-5. Disponible en: http://dx.doi.org/10.1073/pnas.94.26.14930

(18) Dangin M, Boirie Y, Garcia-Rodenas C, Gachon P, Fauquant J, Callier P, et al. The digestion rate of protein is an independent regulating factor of postprandial protein retention. Am J Physiol Endocrinol Metab. 2001 Feb;280(2):E340-8. Disponible en: http://dx.doi.org/10.1152/ajpendo.2001.280.2.E340

(19) Harper AE, Miller RH, Block KP. Branched-chain amino acid metabolism. Annu Rev Nutr. 1984;4:409-54. Disponible en: http://dx.doi.org/10.1146/annurev.nu.04.070184.002205

(20) Stipanuk, Martha H., and Marie A. Caudill. Biochemical, physiological, and molecular aspects of human nutrition-E-book. Elsevier health sciences, 2018.

(21) Jahan-Mihan A, Luhovyy BL, El Khoury D, Anderson GH. Dietary proteins as determinants of metabolic and physiologic functions of the gastrointestinal tract. Nutrients. 2011 May;3(5):574-603. Disponible en: http://dx.doi.org/10.3390/nu3050574

(22) Brosnan JT, Brosnan ME. Branched-chain amino acids: enzyme and substrate regulation. J Nutr. 2006 Jan;136(1 Suppl):207S-11S. Disponible en: http://dx.doi.org/10.1093/jn/136.1.207S

(23) Holeček M. Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. Nutr Metab (Lond). 2018 May 3;15:33. Disponible en: http://dx.doi.org/10.1186/s12986-018-0271-1

(24) Blomstrand E, Eliasson J, Karlsson HK, Köhnke R. Branched-chain amino acids activate key enzymes in protein synthesis after physical exercise. J Nutr. 2006 Jan;136(1 Suppl):269S-73S. Disponible en: http://dx.doi.org/10.1093/jn/136.1.269S

(25) Wolfe RR. Branched-chain amino acids and muscle protein synthesis in humans: myth or reality? J Int Soc Sports Nutr. 2017 Aug 22;14:30. Disponible en: http://dx.doi.org/10.1186/s12970-017-0184-9

(26) Nie C, He T, Zhang W, Zhang G, Ma X. Branched Chain Amino Acids: Beyond Nutrition Metabolism. Int J Mol Sci. 2018 Mar 23;19(4):954. Disponible en: http://dx.doi.org/10.3390/ijms19040954

(27) Zhang S, Zeng X, Ren M, Mao X, Qiao S. Novel metabolic and physiological functions of branched chain amino acids: a review. J Anim Sci Biotechnol. 2017 Jan 23;8:10. Disponible en: http://dx.doi.org/10.1186/s40104-016-0139-z

(28) Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014 May 17;383(9930):1749-61. Disponible en: http://dx.doi.org/10.1016/S0140-6736(14)60121-5

(29) Holecek M, Kandar R, Sispera L, Kovarik M. Acute hyperammonemia activates branched-chain amino acid catabolism and decreases their extracellular concentrations: different sensitivity of red and white muscle. Amino Acids. 2011 Feb;40(2):575-84. Disponible en: http://dx.doi.org/10.1007/s00726-010-0679-z

(30) Holeček M. Branched-chain amino acid supplementation in treatment of liver cirrhosis: Updated views on how to attenuate their harmful effects on cataplerosis and ammonia formation. Nutrition. 2017 Sep;41:80-85. Disponible en: http://dx.doi.org/10.1016/j.nut.2017.04.003

(31) Nishitani S, Takehana K, Fujitani S, Sonaka I. Branched-chain amino acids improve glucose metabolism in rats with liver cirrhosis. Am J Physiol Gastrointest Liver Physiol. 2005 Jun;288(6):G1292-300. Disponible en: http://dx.doi.org/10.1152/ajpgi.00510.2003

(32) Gluud LL, Dam G, Borre M, Les I, Cordoba J, Marchesini G, et al. Oral branched-chain amino acids have a beneficial effect on manifestations of hepatic encephalopathy in a systematic review with meta-analyses of randomized controlled trials. J Nutr. 2013 Aug;143(8):1263-8. Disponible en: http://dx.doi.org/10.3945/jn.113.174375

(33) Tsien C, Davuluri G, Singh D, Allawy A, Ten Have GA, Thapaliya S, et al. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. Hepatology. 2015 Jun;61(6):2018-29. Disponible en: http://dx.doi.org/10.1002/hep.27717

(34) Rodney S, Boneh A. Amino Acid Profiles in Patients with Urea Cycle Disorders at Admission to Hospital due to Metabolic Decompensation. JIMD Rep. 2013;9:97-104. Disponible en: http://dx.doi.org/10.1007/8904_2012_186

(35) Holecek M. Evidence of a vicious cycle in glutamine synthesis and breakdown in pathogenesis of hepatic encephalopathy-therapeutic perspectives. Metab Brain Dis. 2014 Mar;29(1):9-17. Disponible en: http://dx.doi.org/10.1007/s11011-013-9428-9

(36) Holecek M, Sprongl L, Tilser I, Tichý M. Leucine and protein metabolism in rats with chronic renal insufficiency. Exp Toxicol Pathol. 2001 Apr;53(1):71-6. Disponible en: http://dx.doi.org/10.1078/0940-2993-00171

(37) Garibotto G, Paoletti E, Fiorini F, Russo R, Robaudo C, Deferrari G, et al. Peripheral metabolism of branched-chain keto acids in patients with chronic renal failure. Miner Electrolyte Metab. 1993;19(1):25-31.

(38) Cano NJ, Fouque D, Leverve XM. Application of branched-chain amino acids in human pathological states: renal failure. J Nutr. 2006 Jan;136(1 Suppl):299S-307S. Disponible en: http://dx.doi.org/10.1093/jn/136.1.299S

(39) Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. Am J Clin Nutr. 2013 Jun;97(6):1163-77. Disponible en: http://dx.doi.org/10.3945/ajcn.112.036418

(40) Scaini G, Jeremias IC, Morais MO, Borges GD, Munhoz BP, Leffa DD, et al. DNA damage in an animal model of maple syrup urine disease. Mol Genet Metab. 2012 Jun;106(2):169-74. Disponible en: http://dx.doi.org/10.1016/j.ymgme.2012.04.009

(41) Frazier DM, Allgeier C, Homer C, Marriage BJ, Ogata B, Rohr F, et al. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab. 2014 Jul;112(3):210-7. Disponible en: http://dx.doi.org/10.1016/j.ymgme.2014.05.006

(42) Felig P, Marliss E, Cahill GF Jr. Plasma amino acid levels and insulin secretion in obesity. N Engl J Med. 1969 Oct 9;281(15):811-6. Disponible en: http://dx.doi.org/10.1056/NEJM196910092811503

(43) 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 Apr;17(4):448-53. Disponible en: http://dx.doi.org/10.1038/nm.2307

(44) White PJ, Lapworth AL, An J, Wang L, McGarrah RW, Stevens RD, et al. Branched-chain amino acid restriction in Zucker-fatty rats improves muscle insulin sensitivity by enhancing efficiency of fatty acid oxidation and acyl-glycine export. Mol Metab. 2016 Apr 22;5(7):538-551. Disponible en: http://dx.doi.org/10.1016/j.molmet.2016.04.006

(45) She P, Van Horn C, Reid T, Hutson SM, Cooney RN, Lynch CJ. Obesity-related elevations in plasma leucine are associated with alterations in enzymes involved in branched-chain amino acid metabolism. Am J Physiol Endocrinol Metab. 2007 Dec;293(6):E1552-63. Disponible en: http://dx.doi.org/10.1152/ajpendo.00134.2007

(46) Jachthuber Trub C, Balikcioglu M, Freemark M, Bain J, Muehlbauer M, Ilkayeva O, White PJ, Armstrong S, Østbye T, Grambow S, Gumus Balikcioglu P. Impact of lifestyle Intervention on branched-chain amino acid catabolism and insulin sensitivity in adolescents with obesity. Endocrinol Diabetes Metab. 2021 Apr 1;4(3):e00250. Disponible en: http://dx.doi.org/10.1002/edm2.250

(47) Felig P, Marliss E, Cahill GF Jr. Are plasma amino acid levels elevated in obesity? N Engl J Med. 1970 Jan 15;282(3):166. Disponible en: http://dx.doi.org/10.1056/nejm197001152820315

(48) Aronne LJ, Segal KR. Adiposity and fat distribution outcome measures: assessment and clinical implications. Obes Res. 2002 Nov;10 Suppl 1:14S-21S. Disponible en: http://dx.doi.org/10.1038/oby.2002.184

(49) Boden G, Homko C, Barrero CA, Stein TP, Chen X, Cheung P, Fecchio C, Koller S, Merali S. Excessive caloric intake acutely causes oxidative stress, GLUT4 carbonylation, and insulin resistance in healthy men. Sci Transl Med. 2015 Sep 9;7(304):304re7. Disponible en: http://dx.doi.org/10.1126/scitranslmed.aac4765

(50) Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest. 2011 Jun;121(6):2111-7. Disponible en: http://dx.doi.org/10.1172/JCI57132

(51) McLaughlin T, Ackerman SE, Shen L, Engleman E. Role of innate and adaptive immunity in obesity-associated metabolic disease. J Clin Invest. 2017 Jan 3;127(1):5-13. Disponible en: http://dx.doi.org/10.1172/JCI88876

(52) Khan T, Muise ES, Iyengar P, Wang ZV, Chandalia M, Abate N, Zhang BB, Bonaldo P, Chua S, Scherer PE. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI.

Mol Cell Biol. 2009 Mar;29(6):1575-91. Disponible en: http://dx.doi.org/10.1128/MCB.01300-08

(53) Lanthier N, Molendi-Coste O, Horsmans Y, van Rooijen N, Cani PD, Leclercq IA. Kupffer cell activation is a causal factor for hepatic insulin resistance. Am J Physiol Gastrointest Liver Physiol. 2010 Jan;298(1):G107-16. Disponible en: http://dx.doi.org/10.1152/ajpgi.00391.2009

(54) Obstfeld AE, Sugaru E, Thearle M, Francisco AM, Gayet C, Ginsberg HN, Ables EV, Ferrante AW Jr. C-C chemokine receptor 2 (CCR2) regulates the hepatic recruitment of myeloid cells that promote obesity-induced hepatic steatosis. Diabetes. 2010 Apr;59(4):916-25. Disponible en: http://dx.doi.org/10.2337/db09-1403

(55) Wu H, Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. J Clin Invest. 2017 Jan 3;127(1):43-54. Disponible en: http://dx.doi.org/10.1172/JCI88880

(56) Kim E, Goraksha-Hicks P, Li L, Neufeld TP, Guan KL. Regulation of TORC1 by Rag GTPases in nutrient response. Nat Cell Biol. 2008 Aug;10(8):935-45. Disponible en: http://dx.doi.org/10.1038/ncb1753

(57) Sancak Y, Bar-Peled L, Zoncu R, Markhard AL, Nada S, Sabatini DM. Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. Cell. 2010 Apr 16;141(2):290-303. Disponible en: http://dx.doi.org/10.1016/j.cell.2010.02.024

(58) Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017 Mar 9;168(6):960-976. Disponible en: http://dx.doi.org/10.1016/j.cell.2017.02.004

(59) Mark H, Peroni O, Kahn B. Adipose-Specific Overexpression of Glut4 Causes Hypoglycemia by Altering Branched-Chain Amino Acid Metabolism. Diabetes. 2006. 55;1331-P. Disponible en: http://dx.doi.org/10.1152/ajpendo.00116.2005

(60) Yoon MS. The Emerging Role of Branched-Chain Amino Acids in Insulin Resistance and Metabolism. Nutrients. 2016 Jul 1;8(7):405. Disponible en: http://dx.doi.org/10.3390/nu8070405

(61) Joshi MA, Jeoung NH, Obayashi M, Hattab EM, Brocken EG, Liechty EA, et al. Impaired growth and neurological abnormalities in branched-chain alpha-keto acid dehydrogenase kinase-deficient mice. Biochem J. 2006 Nov 15;400(1):153-62. Disponible en: http://dx.doi.org/10.1042/BJ20060869

(62) She P, Reid TM, Bronson SK, Vary TC, Hajnal A, Lynch CJ, et al. Disruption of BCATm in mice leads to increased energy expenditure associated with the activation of a futile protein turnover cycle. Cell Metab. 2007 Sep;6(3):181-94. Disponible en: http://dx.doi.org/10.1016/j.cmet.2007.08.003

(63) Jang C, Oh SF, Wada S, Rowe GC, Liu L, Chan MC, et al. A branched-chain amino acid metabolite drives vascular fatty acid transport and causes insulin resistance. Nat Med. 2016 Apr;22(4):421-6. Disponible en: http://dx.doi.org/10.1038/nm.4057

(64) Shimomura Y, Honda T, Shiraki M, Murakami T, Sato J, Kobayashi H, et al. Branched-chain amino acid catabolism in exercise and liver disease. J Nutr. 2006 Jan;136(1 Suppl):250S-3S. Disponible en: http://dx.doi.org/10.1093/jn/136.1.250S

(65) Newgard CB. Interplay between lipids and branched-chain amino acids in development of insulin resistance. Cell Metab. 2012 May 2;15(5):606-14. Disponible en: http://dx.doi.org/10.1016/j.cmet.2012.01.024

(66) Macotela Y, Emanuelli B, Bång AM, Espinoza DO, Boucher J, Beebe K, et al. Dietary leucine--an environmental modifier of insulin resistance acting on multiple levels of metabolism. PLoS One. 2011;6(6):e21187. Disponible en: http://dx.doi.org/10.1371/journal.pone.0021187

(67) Hinault C, Mothe-Satney I, Gautier N, Lawrence JC Jr, Van Obberghen E. Amino acids and leucine allow insulin activation of the PKB/mTOR pathway in normal adipocytes treated with wortmannin and in adipocytes from db/db mice. FASEB J. 2004 Dec;18(15):1894-6. Disponible en: http://dx.doi.org/10.1096/fj.03-1409fje

(68) Suryawan A, Hawes JW, Harris RA, Shimomura Y, Jenkins AE, Hutson SM. A molecular model of human branched-chain amino acid metabolism. Am J Clin Nutr. 1998 Jul;68(1):72-81. Disponible en: http://dx.doi.org/10.1093/ajcn/68.1.72

(69) Luzi L, Castellino P, DeFronzo RA. Insulin and hyperaminoacidemia regulate by a different mechanism leucine turnover and oxidation in obesity. Am J Physiol. 1996 Feb;270(2 Pt 1):E273-81. Disponible en: http://dx.doi.org/10.1152/ajpendo.1996.270.2.E273

(70) Asghari G, Farhadnejad H, Teymoori F, Mirmiran P, Tohidi M, Azizi F. High dietary intake of branched-chain amino acids is associated with an increased risk of insulin resistance in adults. J Diabetes. 2018 May;10(5):357-364. Disponible en: http://dx.doi.org/10.1111/1753-0407.12639

(71) 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 Oct;45(5):1482-1492. Disponible en: http://dx.doi.org/10.1093/ije/dyw143

(72) Woo SL, Yang J, Hsu M, Yang A, Zhang L, Lee RP, et al. Effects of branched-chain amino acids on glucose metabolism in obese, prediabetic men and women: a randomized, crossover study. Am J Clin Nutr. 2019 Jun 1;109(6):1569-1577. Disponible en: http://dx.doi.org/10.1093/ajcn/nqz024

(73) Neis EP, Dejong CH, Rensen SS. The role of microbial amino acid metabolism in host metabolism. Nutrients. 2015 Apr 16;7(4):2930-46. Disponible en: http://dx.doi.org/10.3390/nu7042930

(74) 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 Oct 15;178(8):1226-32. Disponible en: http://dx.doi.org/10.1093/aje/kwt112

(75) Okekunle AP, Wu X, Duan W, Feng R, Li Y, Sun C. Dietary Intakes of Branched-Chained Amino Acid and Risk for Type 2 Diabetes in Adults: The Harbin Cohort Study on Diet, Nutrition and Chronic Non-Communicable Diseases Study. Can J Diabetes. 2018 Oct;42(5):484-492.e7. Disponible en: http://dx.doi.org/10.1016/j.jcjd.2017.12.003

(76) Karusheva Y, Koessler T, Strassburger K, Markgraf D, Mastrototaro L, Jelenik T, et al. Short-term dietary reduction of branched-chain amino acids reduces meal-induced insulin secretion and modifies microbiome composition in type 2 diabetes: a randomized controlled crossover trial. Am J Clin Nutr. 2019 Nov 1;110(5):1098-1107. Disponible en: http://dx.doi.org/10.1093/ajcn/nqz191

(77) Lamiquiz-Moneo I, Bea AM, Palacios-Pérez C, Miguel-Etayo P, González-Gil EM, López-Ariño C, et al. Effect of Lifestyle Intervention in the Concentration of Adipoquines and Branched Chain Amino Acids in Subjects with High Risk of Developing Type 2 Diabetes: Feel4Diabetes Study. Cells. 2020 Mar 12;9(3):693. Disponible en: http://dx.doi.org/10.3390/cells9030693

(78) Ruiz-Canela M, Guasch-Ferré M, Toledo E, Clish CB, Razquin C, Liang L, et al. Plasma branched chain/aromatic amino acids, enriched Mediterranean diet and risk of type 2 diabetes: case-cohort study within the PREDIMED Trial. Diabetologia. 2018 Jul;61(7):1560-1571. Disponible en: http://dx.doi.org/10.1007/s00125-018-4611-5

(79) Cavallaro NL, Garry J, Shi X, Gerszten RE, Anderson EJ, Walford GA. A pilot, short-term dietary manipulation of branched chain amino acids has modest influence on fasting levels of branched chain amino acids. Food Nutr Res. 2016 Jan 14;60:28592. Disponible en: http://dx.doi.org/10.3402/fnr.v60.28592

(80) 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 Dec 30;13(1):95. Disponible en: http://dx.doi.org/10.3390/nu13010095

(81) Xuan L, Hou Y, Wang T, Li M, Zhao Z, Lu J, et al. Association of branched chain amino acids related variant rs1440581 with risk of incident diabetes and longitudinal changes in insulin resistance in Chinese. Acta Diabetol. 2018 Sep;55(9):901-908. Disponible en: http://dx.doi.org/10.1007/s00592-018-1165-4

(82) Wang W, Jiang H, Zhang Z, Duan W, Han T, Sun C. Interaction between dietary branched-chain amino acids and genetic risk score on the risk of type 2 diabetes in Chinese. Genes Nutr. 2021 Mar 4;16(1):4. Disponible en: http://dx.doi.org/10.1186/s12263-021-00684-6

(83) Wang W, Liu Z, Liu L, Han T, Yang X, Sun C. Genetic predisposition to impaired metabolism of the branched chain amino acids, dietary intakes, and risk of type 2 diabetes. Genes Nutr. 2021 Nov 2;16(1):20. Disponible en: http://dx.doi.org/10.1186/s12263-021-00695-3

(84) Shou J, Chen PJ, Xiao WH. The Effects of BCAAs on Insulin Resistance in Athletes. J Nutr Sci Vitaminol (Tokyo). 2019;65(5):383-389. Disponible en: http://dx.doi.org/10.3177/jnsv.65.383

(85) Glynn EL, Piner LW, Huffman KM, Slentz CA, Elliot-Penry L, AbouAssi H, et al. Impact of combined resistance and aerobic exercise training on branched-chain amino acid turnover, glycine metabolism and insulin sensitivity in overweight humans. Diabetologia. 2015 Oct;58(10):2324-35. Disponible en: http://dx.doi.org/10.1007/s00125-015-3705-6

Receipt date: 12/11/2021
Revision date: 12/16/2021
Acceptance date: 02/15/2022