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IMPACT OF BRANCHED-CHAIN AMINO ACID (BCAA) INTAKE ON TYPE 2 DIABETES MELLITUS

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Summary: Elevated circulating levels of branched-chain amino acids (BCAA) have been described as a strong predictor of type 2 diabetes mellitus (DM2). The main objective is to assess whether a diet rich in these amino acids poses a risk for the development of DM2. Material and methods: This bibliographic review was based on scientific articles selected from different databases. A total of 23 articles were studied in depth. Results and discussion: A higher intake of BCAAs has shown a positive association with DM2, mainly if it comes from foods of animal origin. Also, their selective restriction improves the pathophysiology of DM2 without compromising the intake of other essential nutrients. On the contrary, supplementation with BCAAs has no negative health repercussions. Conclusion: BCAA intake does appear to be associated with an increased risk of DM2; however, this association cannot be studied in isolation, but must be considered part of a complex interaction of dietary components, in which the nutritional quality of the food plays an important role.

Key words: Diabetes Mellitus type 2, insulin resistance, branched chain amino acids, BCAA, dietary intake, supplementation.

IMPACTO DEL CONSUMO DE AMINOÁCIDOS DE CADENA RAMIFICADA (BCAA) EN LA DIABETES MELLITUS TIPO 2

Resumen: Niveles circulantes elevados de aminoácidos de cadena ramificada (BCAA) han sido descritos como un fuerte factor predictor de la diabetes mellitus tipo 2 (DM2). El principal objetivo es evaluar si una dieta rica en estos aminoácidos supone un riesgo para el desarrollo de DM2. Material y métodos: Esta revisión bibliográfica se ha sustentado en artículos científicos seleccionados de diferentes bases de datos.

Un total de 23 artículos fueron estudiados en profundidad. Resultados y discusión: Una mayor ingesta de BCAA ha presentado una asociación positiva con la DM2, principalmente si esta proviene de alimentos de origen animal. Asimismo, su restricción selectiva mejora la fisiopatología de la DM2 sin comprometer la ingesta de otros nutrientes esenciales. Al contrario, la suplementación con BCAA no presenta repercusiones negativas para la salud. Conclusión: La ingesta de BCAA si parece estar asociada a un mayor riesgo de padecer DM2; pero esta asociación no puede estudiarse de forma aislada, sino que debe considerarse parte de una interacción compleja de componentes dietéticos, en la cual, la calidad nutricional de los alimentos adquiere un importante papel.

Palabras clave: Diabetes Mellitus tipo 2, resistencia a la insulina, aminoácidos de cadena ramificada, BCAA, ingesta dietética, suplementación.

Introduction

Diabetes Mellitus (DM) refers to the group of metabolic diseases characterized by alterations in the secretion or action of insulin, inducing one of the most characteristic signs of the disease, hyperglycemia. DM can be classified into four general categories: type 1 diabetes mellitus (DM1), type 2 diabetes mellitus (DM2), gestational diabetes (GD) and diabetes secondary to other comorbidities (1).

Among the different types of DM, as confirmed by various societies (2-4), DM2 is the most common of all, accounting for approximately 90-95% of all cases of diabetes. The pathophysiology of this disease is characterized by the presence of insulin resistance (IR) and deficient insulin secretion. In this case, symptoms usually begin slowly and at a lower intensity than in other types of diabetes, consequently, the diagnosis tends to be made late, once complications have already arisen; all this makes early diagnosis a great clinical challenge (5-7).

Currently the diagnostic techniques used are based on a fasting blood glucose test, a glucose tolerance test or an analysis of glycosylated hemoglobin (HbA1c) (1,6,8), these techniques are useful for identifying the disease once pathophysiological changes in blood glucose homeostasis have already occurred; and, therefore, it would be interesting to detect new markers that serve as early indicators of the disease. For this reason, biomedical research based on metabolomics has intensified in recent years to discover new biomarkers that facilitate the early diagnosis of DM2; among those studied, branched-chain amino acids (BCAA) stand out (9-11).

BCAAs (valine, leucine and isoleucine) are a type of essential amino acids (EAA) of great metabolic relevance, which participate in processes ranging from protein synthesis to insulin secretion (12). Today, a great deal of research (9-11) has been devoted to studying the role of these amino acids in the body. Among the findings, elevated circulating levels of BCAAs stand out as a strong predictor of numerous diseases, including DM2. There is some uncertainty as to the origin of this increase and, therefore, the hypothesis arises as to whether their dietary intake could have some kind of influence, taking into account that the only source of these amino acids is through food. The current evidence concerning the link between dietary BCAAs and their circulating levels seems to be unclear (13-15).

The objective of the present literature review is to evaluate whether a diet rich in branched-chain amino acids (BCAA) poses a risk for the development of Type 2 Diabetes Mellitus; in turn, we also aim to identify whether a dietary restriction of BCAA could have a preventive effect on the development of DM2.

Method

A bibliographic search of scientific articles was carried out through different databases; during the period from January to April 2022. Studies in children, pregnant women, case reports and abstracts or letters to the editor were excluded, giving priority to human trials, review articles and meta-analyses.

The database that mainly supported this research was PubMed; the Cochrane Library and Google Scholar were used in a complementary manner. A keyword search strategy was applied, facilitating the identification of the research, among which "Type 2 Diabetes Mellitus", "insulin resistance", "branched chain amino acids", "BCAA", "dietary intake" and "supplementation" stand out.

Results

Dietetic-nutritional treatment of DM2

Nutritional therapy is a basic component in the approach to DM2; despite this, there is currently no clear consensus on the optimal proportion of macronutrients (carbohydrates, proteins and fats) to be maintained by people with DM2 in order to optimize glycemic control; this is why numerous researchers have become involved in the task of elucidating what type of dietary pattern may be the most appropriate for DM2 (6,16,17).

In a meta-analysis, conducted by Papamichou D. *et. al*. (18) compared the medium- to long-term effectiveness of different dietary patterns for the management of DM2. The authors conclude that the most effective dietary patterns for improving glycemic control and cardiovascular risk factors, taking adherence into account, are the vegetarian and Mediterranean diets. These results are also confirmed in another meta-analysis, Schwingshackl L. *et. al*. (19), which establishes that the dietary pattern based on a Mediterranean diet is the most effective in controlling the pathophysiology of DM2.

In another review, by Lewgood J. *et. al*. (20) conclude that the Mediterranean diet is ideal for the improvement of metabolic health and the adequate management of DM2 and that a plant-based diet (vegetarian or vegan diet) shows promise in the prevention of the disease. On the other hand, they also propose nutritional strategies that may be useful in the short term, such as caloric deficit and low-carbohydrate diets, although further research is required to confirm their effects in DM2 (Figure 1).

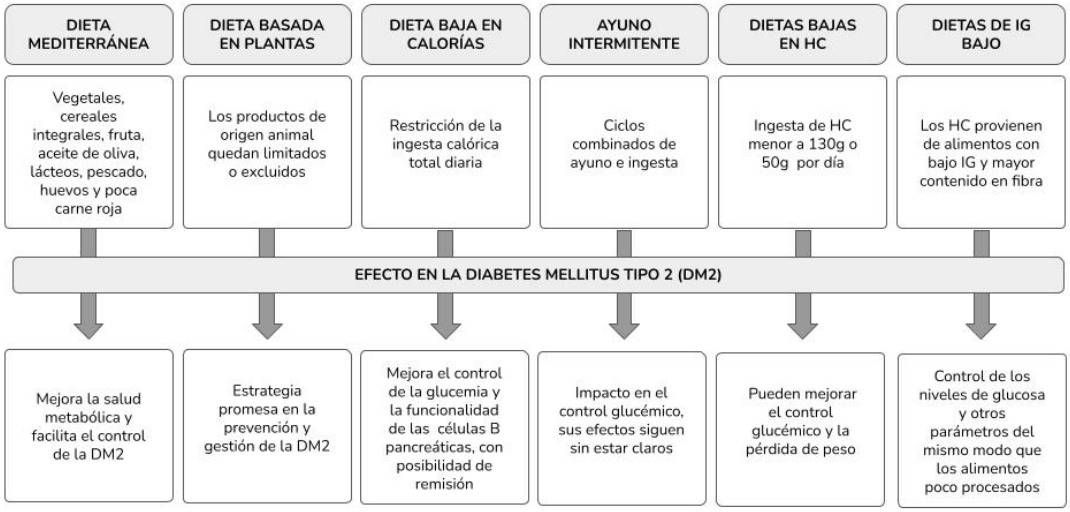


Figure 1. Dietary strategies and outcomes for the management of DM2. Source: Adapted from Lewgood J. *et al*. (2020) (20).

In spite of this, alternative dietary patterns are sometimes chosen, among which the use of the high-protein (HP) diet stands out, where protein intake accounts for approximately 30% of the total caloric content of the diet (21). No significant effects on the improvement of glycemic control have been demonstrated (21-24), in fact, a higher protein intake (mainly of animal origin) has been related to a higher prevalence of DM2 due to its involvement in glucose and insulin metabolism (24-26).

Branched-chain amino acid (BCAA) metabolism

BCAAs refer to leucine, isoleucine and valine (Leu:Ile:Val), understood as a single entity, which, as their name suggests, have a branched structure. They are a type of essential amino acids (EAA), i.e. our body is not able to synthesize them, so they must be supplied through the diet. Consequently, under homeostatic conditions, there must be a balance between intake and elimination (12,27,28).

Normal serum values for an adult are set in ranges of: 66-170 µmol/L for leucine, 42-100 µmol/L for isoleucine and 150-310 µmol/L for valine. This would mean an average of 590 µmol/L for total BCAA (29); taking into consideration that 80% of these values are determined by their intake and the remaining 20% are determined by the products of their metabolism (14).

The metabolism of BCAAs differs from other amino acids in that the liver is not the main metabolic destination, due to the absence of BCAA aminotransferases (BCAT). Instead, these are transaminated (transfer of an amino group from an amino acid to an α-keto acid) in other extrahepatic tissues, most notably skeletal muscle, due to its high BCAT activity (30-32). In this process, α-branched chain keto acids (BCKA) originate, which can already be taken up by the liver. At this point they can either go to the protein synthesis process or be oxidized to maintain the BCAA intake-loss balance (12,33).

Because BCAA metabolism occurs primarily in the mitochondria of peripheral tissue, proper mitochondrial functionality will have a significant impact on plasma BCAA levels (26).

For protein synthesis to occur, mainly in skeletal muscle, two essential factors are required: an anabolic signal and sufficient amounts of amino acids. In particular, BCAAs (especially leucine) act as promoters of this anabolic signal, which explains their growing interest as an ergogenic aid in sport (12). However, they do not act alone, but require other hormonal promoters, such as insulin, to trigger this process. This combination of hormonal and amino acid signals, in turn, coincides with the maximal activation of the mechanistic target of rapamycin (mTOR), the main regulator of cell growth and protein synthesis. Specifically, among the regulatory and signaling functions performed by BCAAs, their significant role in the activation of mTOR should be highlighted (12,31).

As developed above, if BCAAs are not reincorporated into the protein pool, they will be oxidized to maintain balance. This process involves oxidative decarboxylation mediated by the enzyme complex known as branched-chain α-ketoacid dehydrogenase (BCKDH), whose activity is elevated in the liver and decreased in the rest of the body (skeletal muscle, heart, kidney, adipose tissue and brain). The final products obtained in the process are acetyl-CoA and succinyl-CoA; these participate in the course of the Krebs cycle, whose purpose is to produce adenosine triphosphate (ATP), the energy nucleotide par excellence (30,31).

Following a logical sequence, this oxidation process will be enhanced after ingestion. However, there are other processes that can favor its increase, such as exercise or starvation (12,32). The following image (Figure 2) shows a schematic representation of all the processes mentioned above.

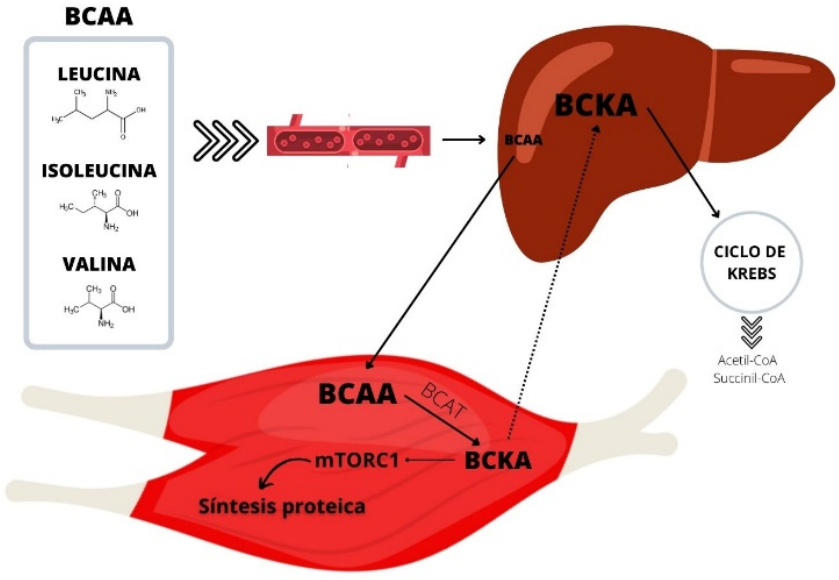


Figure 2. Metabolism of BCAAs, which, after entering the body through food, are used both to synthesize proteins and to be degraded in the Krebs cycle to obtain other secondary metabolites. *Source*: Own elaboration.

BCAA and Insulin Resistance (IR)

The first studies reporting alterations in circulating BCAA levels in patients with diabetes or insulin resistance date back to the 1960s (35,36). Since then, biomedical research devoted to the study of this phenomenon has intensified, although the origins of

this increase in BCAA in the pathophysiology of DM2, especially its correlation with IR, are still under discussion (13,14).

The most relevant and common characteristic in the pathology of DM2 is IR; a condition in which the cells stop responding adequately to this hormone, requiring increasing amounts to produce the same effect. This situation, maintained over time, promotes hyperglycemia, the main clinical symptom of DM2 (1,37). It has become clear that there is a stage prior to IR in which there is dysregulated hyperinsulinemia. In this situation, elevated insulin levels are maintained without causing hypoglycemia, which causes a desensitization of the insulin receptor response (IRS-1) and, consequently, IR occurs (38-40).

Although the correlation between BCAAs and IR has been mentioned many times (12,30,32,33,35,41,42), the underlying mechanisms linking them are not fully understood at present.

On the one hand, the hypothesis that increased BCAA acts as a promoter of IR is supported. This theory is mainly based on the situation of hyperactivation of mTOR (specifically, mTORC-1) caused by the increase in BCAA. This hyperactivation causes an increase in insulin receptor degradation (IRS-1) and a decrease in insulin sensitizing hormone (FGF21) interfering with insulin signaling (30,32-34,41,43). In turn, insulin signaling is also altered by inflammation and oxidative stress, triggered by the storage of lipids in muscles caused by BCAAs and their metabolites (32,34,42,44).

1. Conversely, there is also the theory that it is, in the first instance, the IR that induces the increase in BCAAs. Some of the mechanisms that cause its increase can be summarized as: a situation of systemic hyperinsulinemia due to IR, the presence of genetic markers that induce IR (42) and, finally, it is proposed that the first trigger for its increase arises from the presence of IR at the cerebral level (31).

A recent review by White P.J. *et. al*. (42) provides a comprehensive view of the BCAA-RI association, in which all the mechanisms mentioned above are included. The authors propose that, in the early stages of DM2, in which IR is already present, elevations in BCAA levels occur. These elevations are mediated by the presence of predisposing genetic variants, high levels of adiposity (especially abdominal), alterations of its metabolism in the liver and alterations in the microbiota. BCAAs, once elevated, contribute to the development of disease phenotypes through lipid accumulation in muscle, hyperactivation of protein synthesis mechanisms (mTOR) or depletion of tryptophan levels leading to hyperphagia and behavioral changes.

Finally, most studies (12,30-33,43) conclude that the BCAA-RI ratio arises from an impaired BCAA catabolic pathway, leading to its accumulation in blood. In fact, it has been suggested to use BCAA signaling and metabolism pathways as therapeutic targets for the treatment of IR (43).

Intestinal Microbiota and BCAA

Interestingly, the intestinal microbiota also plays an important role in the pathological increase of circulating BCAA levels. The intestinal microbiota forms a complex ecosystem in the gastrointestinal tract, which is constituted by different microorganisms (bacteria, archaea, viruses, fungi, protozoa...) (45-48).

Like the diet, the microbiota is a substantial source of these nutrients. In fact, a difference has been reported between the microorganisms present in the microbiota of patients with DM2 and those of healthy individuals, which show a greater biosynthesis of BCAAs and repression of their degradation (45,49). Therefore, targeting the metabolism of BCAA produced in the microbiota through dietary intervention could show promise in the prevention and treatment of DM2 (49).

Dietary intake of BCAA and DM2

BCAA's are in a 2:1:1 ratio (Leu:Ile:Val), i.e. for every 4g of BCAA's, 2g of leucine, 1g of isoleucine and 1g of valine are included. Thus, it has been established that the average daily requirements for healthy adults are 40, 20 and 20 mg/kg body weight/day, respectively, for a total of 80 mg/kg body weight/day (50).

Given the close link between circulating BCAAs and DM2, a diet rich in these amino acids could be a risk factor for the development of the pathology, and consequently, their selective restriction could be part of a good strategy to restore metabolic health (13,14,51,52).

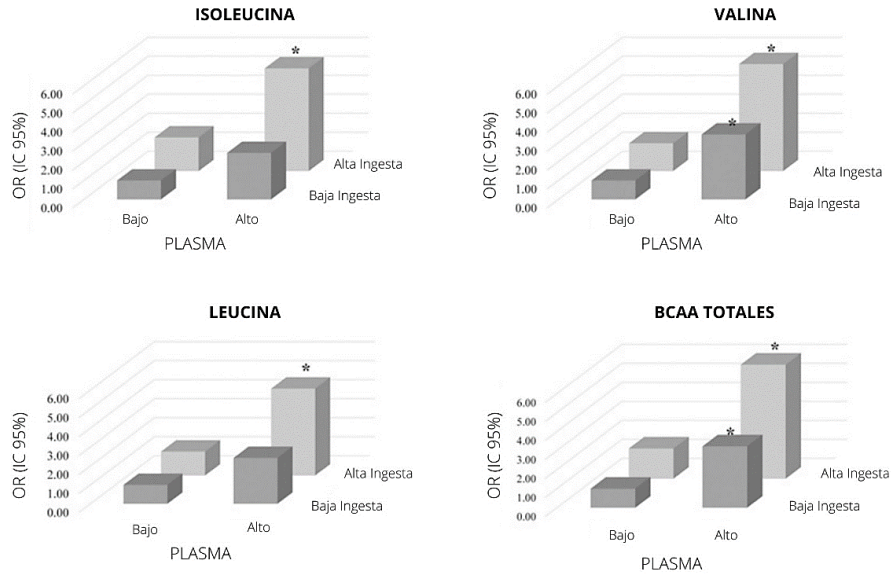
Discussion

On the one hand, observational studies (longitudinal, cross-sectional, cohort and case-control studies) (26,52,15,53,14,54-57) aimed to clarify whether a higher BCAA intake was related to an increased risk of DM2; for this purpose, validated frequency of consumption questionnaires (FFQ) were used to estimate total BCAA intake. Their plasma levels were evaluated through a blood test performed under fasting conditions and the estimation of diabetes risk was measured through the HOMA-IR index. These had a variable durability between six weeks and three years.

Combining all the information gathered in the different investigations, it has been shown that the dietary pattern plays an important role in the amount of BCAA ingested and their circulating levels. On the one hand, it was found that BCAA intake comes mainly from meat, more specifically from red meat and derivatives (26,52,57); this reflects the high consumption of this type of product in the population compared to other protein sources, especially compared to proteins of vegetable origin (legumes, soy...); a dietary pattern which has been associated on numerous occasions with a higher prevalence of diseases and with an intensification of hyperinsulinemia prior to IR (39).

Wang W. *et. al*. (53) argued that high BCAA intake only had negative repercussions in those with a genetic susceptibility to DM2; a statement that is also mentioned in a recent meta-analysis by Supruniuk E. *et. al*. (34). It is hypothesized that those at risk for DM2 have a reduced mitochondrial capacity to catabolize BCAAs, manifesting in an increase in circulating BCAAs. Therefore, under this condition, if BCAA intake is high, it will likewise increase the mitochondrial oxidation load, eventually saturating its system and causing catabolism dysfunction, as well as poor insulin action. On the contrary, in those individuals with an adequate mitochondrial capacity to catabolize BCAAs, these amino acids may have beneficial effects on health, especially muscle protein synthesis (34,53). Similarly, in the research carried out by Tobias D.K. *et. al.* (54) did not obtain a significant trend in the interaction of intake and serum BCAA concentrations when these were at normal values; but they did in those with high plasma concentrations (Figure 3).

Figure 3. Joint representation between circulating levels of BCAAs (low versus



high) and dietary intake of BCAAs (low versus high). *Source*: Adapted from Tobias D.K. *et. al*. (2018) (54).

In this same context, we must take into account the important role played by the catabolic process of BCAAs in their circulating levels, beyond the fact that intake may also have a modest effect. Therefore, elevated circulating BCAA values could reflect an early alteration in protein metabolism, a situation that is worsened if a high BCAA intake is maintained (59).

Meta-analyses and reviews (34,58-60) established a positive association between higher dietary BCAA intake and DM2, with the exception of a meta-analysis conducted by Vieira E.E.S. *et. al*. (13), which claimed to obtain inconsistent results in relation to BCAA intake and DM2 since it did not confirm an impairment of IR; but, in the same way, it supports the metabolic damage that an unhealthy diet presents, producing alterations in BCAA metabolism. It should be noted that this study included only 3 observational studies. All of them explain the importance of taking into account the global computation of dietary behavior and the intervention of environmental factors in the study

population in order to establish a correct interpretation of the impact of BCAA intake on metabolic health.

When studying the impact of a BCAA supplementation protocol, randomized clinical trials (61-63) found no negative effects on glucose metabolism or IR. A meta-analysis performed by Okekunle A.P. *et. al.* (60), which compared the impact of oral BCAA supplementation versus dietary intake in relation to DM2, showed that supplementation had no significant impact on circulating BCAA levels, whereas a higher intake of dietary BCAA was associated with a higher risk of DM2.

On the other hand, the intervention studies (51,64-70) assessed the variations in circulating BCAA and in the parameters indicative of DM2 presented by a reduction in BCAA consumption. The trials had a variable duration between one week and two years and their main objective was to clarify whether this selective restriction could reduce circulating BCAA levels and, consequently, improve DM2 analytical values (serum glucose, HOMA-IR...). In all interventions, BCAA intake was provided through dietary intake and both plasma levels and glycemia were measured through a blood test performed under fasting conditions. Likewise, the estimation of diabetes risk was measured through the HOMA-IR index.

In general terms, after the interventions, favorable results were shown in the reduction of plasma BCAA levels, implying a lower incidence of DM2; with the exception of a study carried out by Prodhan U.K. *et. al*. (68) in which no significant changes in plasma BCAA levels were observed, although this was only limited to assessing the impact of the consumption of dairy products, without assessing overall intake. Importantly, these restrictions did not compromise the intake of other essential nutrients (69).

The intervention carried out by Ruiz Canela M. *et. al*. (67) suggest that a dietary pattern based on the Mediterranean diet could mitigate the adverse effects of elevated plasma BCAA on the development of DM2 and, in turn, contribute to its reduction. The impact of a dietary pattern of transition to a vegan diet, in which fish was included as the only animal protein source, was also discussed. In this research conducted by Elshorbagy A. *et. al*. (56) showed a rapid and sustained decrease in plasma BCAA concentrations; leucine decreased on average by 13.5%, isoleucine by 11% and, finally, valine showed a greater decrease at 19.5%.

Asghari G. *et al*. (14) and Fontana L. *et. al*. (51) did not obtain a significant association in insulin levels or pancreatic β-cell functionality when restricting dietary intake of BCAA; but they did obtain an improvement in IR by increasing insulin-sensitizing hormone (FGF21) levels and a considerable decrease in fasting blood glucose. These results have also been reported in other trials (64,66,67,69) and could indicate a certain reversibility of this physiological situation.

Because obesity is considered one of the main risk factors for DM2, it is interesting to observe what happens to BCAA levels in these patients and how they respond to dietary modifications in these patients. On the one hand, a positive association has been found between the BMI value and circulating BCAA (55,71); in fact, it is proposed that elevated levels of these amino acids, at the same time, can be used as markers of cardiovascular disease (58,72,73); likewise, elevated serum BCAA

concentrations in obese individuals are reversed with weight loss, until adequate values are reached (71). It is true that, in this context, the scientific evidence is inconsistent

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Conclusions

Despite the essential nature of BCAAs, an excessive accumulation of BCAAs or their metabolites in the blood has been correlated with different pathological conditions, among which the IR characteristic of DM2 stands out. The origin of this increase is still unknown; the main hypotheses point in two directions: a high dietary intake of BCAAs or a dysfunction in their catabolism.

A higher intake of BCAAs has shown a positive association with DM2, especially if it comes from animal products; also, their selective restriction contributes to reduce serum levels and improve metabolic health, without compromising the intake of other essential nutrients. In contrast, BCAA supplementation protocols do not have negative health effects.

This contradiction shows that the effects of BCAAs on metabolic health related to DM2 cannot be studied in isolation; rather, they must be considered as part of a complex interaction of dietary components, in which the nutritional quality of the food is of great importance.

These results, once again, demonstrate the important role that nutrition plays in health and disease, and how certain dietary patterns can seriously worsen our health. However, more research is needed to fully study the impact of BCAA intake on health.

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