

The Relationship Between Branched-Chain Amino Acids and Insulin Resistance



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Submission: August 05, 2019; **Published:** September 18, 2019

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Abstract

Obesity is a health problem worldwide and plays a role in the development of insulin resistance. In obese people, there occurs an increase in the level of branched-chain amino acids. Leucine, isoleucine and valine, which are among branched-chain amino acids, are essential amino acids. Branched-chain amino acids may create positive effects on body weight, muscle protein synthesis, and glucose homeostasis regulation. Despite the positive effects of branched-chain amino acids on metabolic health, an increase in their level in the body is associated with the increase in insulin resistance and type 2 diabetes risk. The degradation of branched-chain amino acid catabolism in the adipose tissue in obese individuals may contribute to an increase in the level of branched-chain amino acids in the case of obesity and insulin resistance. Branched-chain amino acids activate mammalian target of rapamycin complex 1 (mTORC1) and thus contribute to the development of insulin resistance. Furthermore, the degradation of branched-chain amino acid catabolism in obese individuals leads to an increase in the amount of toxic metabolites and causes beta cell dysfunction, which results in insulin resistance and glucose intolerance. Branched-chain amino acids, which are among the essential acids, might play a role in the development of insulin resistance. Putting a limitation on branched-chain amino acids in the diets of obese individuals can be considered as one of the precautions to be taken against the development of insulin resistance.

Keywords: Branched-chain amino acids; Leucine; Isoleucine; Valine; Insulin resistance; Adipose tissue; Type 2 diabetes risk; Body weight; Muscle protein synthesis; Glucose homeostasis; Carbohydrates; Proteins; Fats

Abbreviations: BMI : Body Mass Index; BCAA: Branched-Chain Alpha-Keto Acids; PPM1K: Protein Phosphatase 1K; GLUT: Glucose Transporters; BCAT: Branched-Chain Amino Acid Transferase; MSUD: Maple Syrup Urine Disease; mTORC: Mammalian Target of Rapamycin Complex; IRS-2: Insulin Receptor Substrate-2; LAT1; Large Neutral Amino Acid Transporter 2 Receptor

Introduction

Obesity is a global health problem on the rise. It is a significant risk factor for the onset and development of diabetes, metabolic syndrome, cancer and other chronic disorders. Insulin resistance has a significant role in metabolic disorders associated with obesity [1]. Insulin resistance is a metabolic complication of obesity and is an important risk factor for the development of type 2 diabetes and metabolic syndrome [2]. Various mechanisms which include carbohydrates, proteins and fats are deemed responsible for the development of insulin resistance [1]. The increase in the levels of isoleucine, leucine and valine, which are the branched-chain amino acids (BCAA) in circulation, is a contributing factor to the pathogenesis of insulin resistance [2]. Increased BCAA concentration is a frequently observed phenomenon in the cases of obesity and insulin resistance [2-4]. On the other hand, a decrease in the level of these amino acids in the body has positive effects on metabolic health. Reducing

the BCAA content of the diet may quickly reverse obesity which results from malnutrition [3]. Weight loss results in decrease in plasma BCAA concentration and improvement in insulin action [2].

Branched-chain amino acids are essential amino acids. Leucine, isoleucine and valine are included in this group of acids [5-7]. These amino acids are critical nutrients that affect the metabolism directly or indirectly. They exist in dietary proteins in relatively large amounts and constitute 15-20% of protein intake [6]. Branched-chain amino acids make up 35% of essential amino acids in the muscles, 40% of protein need, and 50% of essential amino acids in foods [8]. Unlike most amino acids, the catabolism of branched-chain amino acids does not occur in the liver. This is because the enzyme activity which catalyzes the first step of catabolism is low in the liver. For this reason, these amino acids quickly proliferate in the circulatory system

following the protein intake [7]. After they are taken into the body, the first step of branched-chain amino acids is catalyzed by branched-chain aminotransferase enzyme (BCAT). The skeletal muscle where this enzyme activity takes place abundantly is the location where the greater part of catabolism of branched-chain amino acids happen. Branched-chain aminotransferase enzyme participates in the transfer reaction of the amino group to alpha ketoglutarate for the formation of glutamate [1,7,9]

The next step catalyzes mitochondrial branched-chain alpha-keto acid dehydrogenase complex (BCKDC) multi-enzyme. This enzyme is found in the mitochondrial membrane. Branched-chain acyl CoA esters catalyze decarboxylation of BCKA [1,7,9]. Finally, metabolites of branched-chain amino acids form a final product as a result of a series of enzyme reactions. The formed products enter tricarboxylic acid cycle [9]. The production and activity of branched-chain alpha-keto acid dehydrogenase complex can be changed by several metabolic factors associated with obesity, insulin resistance and type 2 diabetes. The mutation of branched-chain alpha-keto acid dehydrogenase complex and the mitochondrial isoform of its activator, protein phosphatase 1K (PPM1K), leads to the concentration of branched-chain amino acids and branched-chain alpha-keto acids (BCKA) [6]. The changes in branched-chain aminotransferase and branched-chain alpha-keto acid dehydrogenase complex have significant effects on branched-chain amino acid catabolism. During the branched-chain amino acids catabolism process, some toxic intermediates may accumulate. This accumulation may contribute to the impairment of cellular and organic functions. The disruption in the metabolism of branched-chain amino acid might increase the sensitivity to insulin resistance and type 2 diabetes. The increase in toxic branched-chain amino acid metabolites rather than in branched-chain amino acids might lead to mitochondrial dysfunction and beta cell apoptosis [1].

The supplementation of these amino acids or diets rich in branched-chain amino acids may frequently create positive effects on body weight, muscle protein synthesis and the regulation of glucose homeostasis [5,6]. In spite of their positive effects on metabolic health, the increase in the level of branched-chain amino acids in the body is associated with the increase in the risk of insulin resistance and type 2 diabetes [6]. The increase in the level of branched-chain amino acids in the circulatory system contributes to insulin resistance pathogenesis [2,10,11]. The increase in the level of branched-chain amino acids in the diet can yield positive impacts on the parameters associated with obesity and type 2 diabetes. Branched-chain amino acids can regulate hormone secretion which may affect nutrient intake and glycemic level [5].

The level of branched-chain amino acids in obese individuals with insulin resistance is high [2,12-14]. Obese individuals with hyperinsulinemia are prone to have higher branched-chain amino acid concentration [12]. Weight loss can lead to decrease in plasma branched-chain amino acid concentration and

improvement in insulin action [2]. Branched-chain amino acids assume a significant role in the development process of obesity and diabetes [1,12]. In obese individuals, the level of branched-chain amino acids in the circulation increases [15]. The increase in the concentration of branched-chain amino acids in obese individuals results in an increase in the tendency to develop diabetes [12]. The insulin resistance in the skeletal muscle can be caused by the accumulation of lipid species [5]. The increase in branched-chain amino acid concentration stimulates short chain fatty acid production. Short chain fatty acids can change fatty acid metabolism by stimulating leptin production. Thus, short chain fatty acids form an inhibitor effect on the lipolysis of adipocytes and contribute to the development of obesity. Besides, branched-chain amino acids augment the conversion of alanine to pyruvate. Alanine is a highly glucogenic amino acid observed in increased levels in obese patients [12]. The increase in the metabolic products of branched-chain amino acids can affect the accumulation of branched-chain amino acids and the mitochondrial oxidation of glucose and lipids which cause stress [12].

Discussion

Branched-chain amino acids are essential amino acids that should be included in the diet. They not only serve as the basic structure for tissue proteins, but also have other metabolic functions [9]. Branched-chain amino acids, independent of the body mass index (BMI), are considered to be an early indicator of insulin resistance and type 2 diabetes [5,12]. Insulin resistance is described as the impairment of the response to insulin action in the target tissues such as skeletal muscle, adipose tissue and the liver. Insulin resistance causes a decrease in the suppression of hepatic glucose output and impairment of glucose uptake which is mediated by the glucose usage in the skeletal muscle and adipose tissue and insulin [16]. There is a strong correlation between branched-chain amino acids and insulin resistance [9,12,17,18]. These amino acids may help insulin resistance and glucose intolerance to develop. High level of branched-chain amino acids can lead to a decrease in insulin action [19]. In the study conducted by Barceló et al., the serum isoleucine values of the individuals with normal glucose tolerance and the patients with glucose intolerance were determined to be 70 ± 13 $\mu\text{mol/L}$ and 78 ± 16 $\mu\text{mol/L}$, respectively, and the valine values to be 268 ± 41 $\mu\text{mol/L}$ and 286 ± 36 $\mu\text{mol/L}$, respectively. Thus, it was concluded that the serum isoleucine and valine values of the individuals with glucose intolerance were higher than those of the individuals with normal glucose tolerance. In a study carried out by Yamada et al., it was found that there was a positive correlation between HOMA-IR and valine, leucine and isoleucine concentration.

In the same study, the serum leucine, isoleucine and valine concentrations of individuals whose HOMA-IR values were $\leq 1,6$ and $>1,6$ were compared. It was determined that the serum leucine, isoleucine and valine concentrations of the individuals

with HOMA-IR value of $>1,6$ were higher compared to those of the patients with HOMA-IR value of $\leq 1,6$. In their study, Labonte et al. [20] divided the male and female individuals into 3 groups and examined their plasma branched-chain amino acid concentrations. The plasma branched-chain amino acid concentrations of healthy, overweight/obese, and type 2 diabetic males and healthy, overweight/obese, and type 2 diabetic females were determined as 412 ± 48 $\mu\text{mol/L}$, 444 ± 55 $\mu\text{mol/L}$, 446 ± 60 $\mu\text{mol/L}$, 358 ± 45 $\mu\text{mol/L}$, 375 ± 49 $\mu\text{mol/L}$ and 398 ± 42 $\mu\text{mol/L}$, respectively. As a result, it was shown that the plasma branched-chain amino acid levels of the overweight/obese and type 2 diabetic individuals were higher than those of the healthy individuals. It was thus concluded that there was a negative correlation between branched-chain amino acids and insulin resistance.

The oxidation of branched-chain amino acids can result in insulin resistance [21]. The increase in the level of branched-chain amino acids can cause a change in the function of large neutral amino acid transporter 2 receptor (LAT1). These receptors are necessary for the entry of branched-chain and aromatic amino acids into the cell [12]. A diet which includes a low amount of branched-chain amino acids can have a healing effect on insulin resistance [22]. The level of branched-chain amino acids increases in the case of obesity. This increase can be induced by the acceleration of protein catabolism. Degradation of branched-chain amino acid catabolism, especially in adipose tissue, can contribute to an elevation in the level of branched-chain amino acids in the case of obesity and insulin resistance. There occurs a decrease in the production of enzymes which catalyze the first step of this catabolism in obese patients. Thus, the level of plasma branched-chain amino acids increases considerably [16].

There are two potential mechanisms that explain how branched-chain amino acids contribute to the development of insulin resistance in obesity. First of all, the inclusion of branched-chain amino acids in the diet activates mammalian target of rapamycin complex 1 (mTORC1) and can thus lead to the development of insulin resistance and type 2 diabetes [5,6,16,23]. The activation of serine kinases and mTORC1 contributes to the development of insulin resistance by supporting serine phosphorylation of insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2) [1,5,6,16]. Mammalian target of rapamycin (mTOR) is a serine/threonine kinase which belong to the family of phosphatidylinositol kinase dependent (P1) protein kinase. This enzyme can regulate critical cellular and developmental processes such as cell growth, differentiation, survival and metabolism of the cell. Mammalian target of rapamycin has at least two different biochemical and functional complexes. Two of these are mammalian target of rapamycin complex 1 (mTORC1) and mammalian target of rapamycin complex 2 (mTORC2). Mammalian target of rapamycin complex 1 (mTORC1) regulates cell development in intracellular and extracellular events such as cellular energy status and cellular

oxygen level [6]. Among leucine, isoleucine and valine, leucine is the most active amino acid in the activation mTORC signal pathway [9,22]. Leucine supplementation can improve glucose balance [24]. Leucine also has a promoting effect on protein synthesis [9].

Accompanied by lipotoxicity and inflammation associated with insulin resistance, insulin increase resulting from insulin action leads to hyperinsulinemia. Ultimately, euglycemia cannot be maintained and type 2 diabetes becomes evident [5]. The second mechanism which explains how branched-chain amino acids contribute to the development of insulin resistance is based on organic acidemia and maple syrup urine disease (MSUD) studies. In this alternative mechanism, the elevated branched-chain amino acid level in individuals with impaired branched-chain amino acid metabolism is claimed to be an indicator of degraded metabolism. The impairment of branched-chain amino acid can lead to the accumulation of toxic metabolites which induce mitochondrial dysfunction of pancreatic beta cells [5,9]. Rather than the branched-chain amino acids themselves, the accumulation of toxic metabolites can lead to beta cell mitochondrial dysfunction and ultimately to beta cell apoptosis [5]. Monomethyl branched-chain fatty acids (mmBCFA) can provide a connection between branched-chain amino acid metabolism and metabolic dysfunction. In most tissues, branched-chain amino acids are subjected to deamination by mitochondrial branched-chain amino acid transferase (BCAT2 or BCATm) in order to form branched-chain alpha-keto acids. Branched-chain alpha-keto acids are exposed to decarboxylation by branched-chain alpha-keto acid dehydrogenase complex [2]. Visceral adipose tissue plays an important role in the relationship between branched-chain amino acids and insulin resistance. Branched-chain amino acid catabolic gene expression in visceral adipose tissue is in strong correlation with insulin sensitivity. This gene expression is observed to have decreased in obese individuals with metabolic syndrome in comparison to obese individuals without metabolic syndrome [5]. In a study conducted by Reitman et al. [25], branched-chain amino acid level in obese individuals was determined to be higher compared to individuals with normal weight. Branched-chain amino acid level in normal weight individuals was measured as $1,3\pm 0,06$ (AU)($\times 10^7$), whereas it was measured in obese individuals as $1,6\pm 0,08$ (AU)($\times 10^7$). In the same study, it was demonstrated that there was a positive correlation between visceral adipose tissue and isoleucine ($p=0.0004$) and valine ($p=0.0007$).

Branched-chain amino acids can also increase glucose consumption and usage level. These amino acids increase glucose uptake through the activation of glucose transporters (GLUT). Leucine elevates glucose uptake by increasing glucose transporter (GLUT1) and glucose transporter (GLUT3) translocation. Leucine can lead to an increase in glucose transporter 4 (GLUT4) expression. There are two hypotheses which reveal the relationship between leucine and glucose transporters. In the first hypothesis, leucine increases GLUT1

and GLUT4 translocation by reducing insulin level. In the second hypothesis, leucine can increase glucose uptake in the skeletal muscle through phosphatidylinositol 3 kinase and protein kinase C signal pathways associated with GLUT4 translocation. Branched-chain amino acids can regulate the expression and translocation of muscular and intestinal glucose transporters through pathways dependent on or independent from insulin [9].

Conclusion

Branched-chain amino acids are essential amino acids for humans. They are considered among significant nutrition elements not only because they cannot be synthesized in the body but also because of their metabolic and regulatory roles. Metabolic dysfunction of branched-chain amino acids and permanent activation of mTORC1 can establish the connection of branched-chain amino acids with metabolic disease risk. The increase in the level of plasma branched-chain amino acids can lead to degradation and dysfunction of branched-chain amino acid metabolism. Eventually, it can cause mitochondrial dysfunction associated with beta cell apoptosis and stress kinase activation. Beta cell apoptosis and stress kinase activation are associated with insulin resistance and type 2 diabetes. The increase in branched-chain amino acid level constitutes a risk for the development insulin resistance. Reducing the branched-chain amino acid content of obese people's diet can be among the precautions to be taken against insulin resistance.

Acknowledgement

No support was received from any person or institution in the process of writing this article. There is no funding and sponsorship that support the writing of the article.

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DOI: [10.19080/CRDOJ.2019.12.555830](https://doi.org/10.19080/CRDOJ.2019.12.555830)

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