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Research Article

Is Branched Chain Amino Acids a Causative or Diagnostic or Prognostic Marker in Metabolic Syndrome?

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ABSTRACT
The prevalence of metabolic syndrome is increasing throughout the globe due to an alarming rise in the number of people with obesity, diabetes mellitus and hypertension which are contributing to the risk of deaths due to cardiovascular diseases.

The development of insulin resistance, modifications in the effects of insulin and changes in the lipoprotein particles plays a significant role in the progression of its complications. Recently many research studies have emphasized the significant link between branched chain amino acids, insulin resistance and diabetes mellitus.Branched chain amino acids have been implicated in the development of Gestational diabetes mellitus (GDM).

But whether these branched chain amino acids are responsible for the development of insulin resistance or it is due to the resulting consequences of insulin resistance remains controversial. The branched-chain amino transferase (BCAT) is involved in the conversion of branched-chain amino acid (BCAA) into branched-chain keto acids (BCKA) followed by oxidative decarboxylation by the action of branched-chain ketoacid dehydrogenase complex.

This review article discuss in detail the role of branched chain amino acids as a potential novel biomarkers in the causative mechanism, prognosis as well as a diagnostic marker of abnormal glucose metabolism in different conditions.

KEY WORDS: branched chain amino acids, insulin resistance, diabetes mellitus, hypertension, metabolic syndrome

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Introduction / Background:

The prevalence of obesity and diabetes mellitus is rising throughout the world requiring diet, drug and surgical treatment to restore their health. The consumption of high protein content is increased. Branched-chain amino acids (BCAAs) are essential amino acids that are not synthesized in our body and have to be obtained from dietary sources (Siddik MAB et al.,2019). Branched-chain amino acids comprise approximately 35% of all amino acids in muscle proteins and play a vital role in protein synthesis and energy homeostasis, ultimately contributing to muscle mass and physical performance(Fine KS et al., 2024).

Branched-chain amino acids are found to be increased in circulation with obesity, insulin resistance and type 2 diabetes mellitus. It may partially mediate cardiometabolic disease which may serve as the earliest predictive marker for future risk of diabetes mellitus (Fine KS et al., 2024).Obesity, Insulin resistance and type 2 diabetes mellitus contribute to cardiovascular diseases. The understanding of the mechanism of action at the molecular level may help to develop newer treatment strategy to improve the quality of life of the patients.The major source of branched-chain amino acids are dietary intake and certain bacteria within the gut microbiome that are capable of synthesizing them but the production varies among different individuals influenced by various factors like diet, gut microbiome composition and overall health. Branched-chain amino acids supplementation induces dysregulation of glucose metabolism and causes insulin resistance, whereas reduction in their levels by diet, drug or surgical intervention can lead to improvement in insulin sensitivity and glycemic control (Abdualkader AM et al., 2024).

The metabolism of branched-chain amino acids involves their catabolism into branched-chain α-keto acids(BCKAs) through enzymatic steps, primarily occurring in mitochondria.Branched-chain amino acids play a crucial role in signaling pathways and nitrogen balance relevant to cardiometabolic health. Their elevated plasma concentrations have been observed in both obese individuals and animal models of obesity(Abdualkader AM et al., 2024). The plasma concentration of BCAA is regulated by the balance between intake of dietary protein, proteolysis(these two increasing the amino acids levels) and protein synthesis and oxidation (these two decreasing the amino acids levels). Insulin plays a pivotal role in maintaining this balance.

Under normal and healthy conditions, insulin regulates the plasma BCAA concentrations by facilitating the cellular uptake of BCAAs while suppressing proteolysis. But, this regulatory mechanism may be disrupted in pathological states like insulin resistance. Previous research studies on obese females have shown that moderate obesity correlates with increased proteolysis and impaired antiproteolytic effects of insulin. It was suggested that the increased proteolysis seen in obesity and insulin resistance may be due to the compromised antiproteolytic function of insulin (Elżbieta Supruniuk et al., 2023).Additionally, BCAAs provide a rich source of nitrogen for the synthesis of nonessential amino acids and proteins and are particularly important in states of growth, repair and positive nitrogen balance, such as muscle building or recovery from injuries(Fine KS et al., 2024).

The enzyme that catalyzes the first step of branched-chain amino acid (BCAA) catabolism is branched-chain amino transferase (BCAT), which is involved in the synthesis and degradation of leucine, isoleucine and valine. There are two main subtypes of human branched chain amino transferase (hBCAT), including cytoplasmic BCAT (BCAT1) and mitochondrial BCAT (BCAT2). Branched-chain amino acid transferase (BCAT) are enzymes that catalyze the catabolism of branched-chain amino acids (BCAA), catalyzing the transamination of three BCAA to branched-chain keto acids (BCKA). The branched-chain ketoacid dehydrogenase complex catalyzes the oxidative decarboxylation of branched-chain ketoacids to generate branched-chain acyl-CoA intermediates, which are subsequently involved in different metabolic pathways(Chen C et al.,2023, C Nong X et al.,2022, Adonia E et al.,2017, She et al.,2007).

These two enzymes have differences in their physiological functions and regulatory mechanisms. BCAT1 encodes a cytoplasmic protein expressed primarily in the brain that provides nitrogen for cerebral glutamate synthesis and is secondarily expressed in embryonic tissue, the ovaries, the placenta, and neurons of the peripheral nervous system. BCAT2 encodes a mitochondrial protein commonly expressed in almost all organs (Chen C et al.,2023, C Nong X et al.,2022, Adonia E et al.,2017, She et al.,2007).The impaired function of these enzymes either due to primary genetic abnormality or due to acquired effects (due to elevated fatty acids, proinflammatory cytokines etc) may cause accumulation of branched chain amino acids and branched-chain keto acids which may potentiate the development of further insulin resistance(Zachary Bloomgarden 2018).

BCAT transfers the amino group from BCAAs to α-ketoglutarate, producing glutamate and the corresponding branched-chain α-keto acids. This transamination reaction generates ammonia as a byproduct, particularly in the muscles. The muscle activates the alanine cycle to remove excess ammonia by attaching the amino group from glutamate to pyruvate which is converted into alanine. Also, muscles help in ammonia detoxification by converting

glutamate and ammonia into glutamine. Both alanine and glutamine are transported to the liver for the final disposal of ammonia and conversion into urea (Abdualkader AM et al., 2024).

Branched-chain amino acid metabolism is a complicated process that depends on interorgan communication to maintain BCAA homeostasis. Skeletal muscle significantly contributes to the circulating pool of BCAAs and plays a major role in BCAA transamination due to the abundance of BCAT2 within the muscle mass. It not only serves as a hub for BCAA transamination but also act as a major site for BCAA oxidation and protein synthesis. In contrast, the liver lacks BCAT2 in hepatocytes but has high BCKDH activity, that helps in BCAA oxidation(Abdualkader AM et al., 2024). Recent research studies have discovered that brown adipose tissue as an additional significant site for BCAA oxidation. On exposure to cold environment, brown adipose tissue significantly enhances BCAA uptake in this tissue compartment to generate heat through thermogenesis. Previous studies have shown that these inter-organ communication which is very essential to maintain BCAA homeostasis is disturbed in obesity and insulin resistance.(Abdualkader AM et al., 2024).
Branched-chain amino acids (BCAAs) exerts many physiological functions mainly through mammalian target of rapamycin (mTOR) signalling pathway. It plays a role in stimulation of pancreatic insulin secretion, milk production, adipogenesis, and increased immune function (Md Abu Bakkar Siddik et al., 2019). BCAAs, especially leucine, are potent activators of the mTOR (mammalian target of rapamycin) pathway. This is a complex signaling pathway that plays a role in protein synthesis and cell growth (Shah H et al.,2024, Fine KS et al., 2024, Abdualkader AM et al., 2024). Recent studies suggest that endogenous BCAAs, BCAA metabolism and mTOR-related autophagy play important roles in the relationships among BCAAs, longevity, and insulin resistance (Yao H et al.,2023). BCAAs have also been implicated in insulin resistance, lipid metabolism, glutamate dehydrogenase activation, inflammation, and platelet activation pathways (Fine KS et al., 2024).
Obesity can lead to the onset of type 2 diabetes mellitus. Insulin sensitivity is often reduced in obesity and beta cells of pancreas are not able to produce higher insulin secretion for the compensation. Many research studies over the last decade have shown the role played by the catabolism of branched-chain amino acids (BCAA) in the development of insulin resistance in people with obesity and type 2 diabetes mellitus.(Md Abu Bakkar Siddik et al., 2019, Zachary Bloomgarden 2018,Froukje et al., 2022). An hypothesis was suggested linking BCAA metabolism, insulin resistance, type 2 diabetes mellitus and its microvascular complications (Tanase, D.M et al.,2023, Chenghui Zhang et al.,2023, Mahmoud Aet al.,2018). The association of branched-chain amino acids with the risk for future diabetes is at least partly mediated through insulin resistance(Würtz P et al., 2013).

Circulating branched-chain amino acids have consistently shown positive associations with the risk of developing type 2 diabetes mellitus. These amino acids may serve as a novel useful biomarkers in the identification of people at risk of type 2 diabetes mellitus before overt symptoms. Insulin resistance may mediate the relationship between these amino acids and risk of type 2 diabetes mellitus(Chen S et al., 2009).Plasma branched-chain amino acid concentrations are associated with type 2 diabetes mellitus incidence across all temporal subgroups, therefore it was suggested that it can serve as an early biomarker for type 2 diabetes mellitus irrespective of follow-up time (Ramzan, I et al., 2022).The association between branched-chain amino acids and type 2 diabetes mellitus may be influenced by calorie intake(Torki, S.A et al.,2023).
Metabolomic profiling helps to reveal metabolites and metabolic pathways relevant to the pathophysiology of insulin resistance. This may help to identify the persons with risk for diabetes mellitus (Sawicki KT et al.,2023).Metabolomics studies have shown that branched amino acids (BCAAs) are involved in several metabolic pathways of insulin resistance, and they reduce insulin secretion through their effects on beta cells of pancreas(Cynthia Roy et al., 2018, Jelena Omazic 2021, Pappa KI et al., 2007).It was observed in a previous research study that the circulating branched chain amino acids (BCAAs) in normoglycemic middle-aged adults positively correlates with the future risk of diabetes mellitus, but the research focused on middle-aged, high-risk adults largely of European population only (Sawicki KT et al., 2023). BCAA levels are dynamic and modifiable which are suggested by its lowering level in gastric bypass surgical intervention (Abdualkader AM et al., 2024).

BCAA is a useful biomarker for early detection of insulin resistance(IR) and later diabetic risk. The factors like person's race, gender, dietary patterns and genetic variants can influence the levels of branched chain amino acid and their associations with insulin resistance (Xue Zhao et al.,2016). Chronic leucine supplementation significantly improves glycemic control and maintains systemic glucose homeostasis by improving the insulin sensitivity in liver and muscle (Guo et al., 2010, Jingfei Zhang et al.2019). Serum BCAA shows an independent correlation with the parameters that indicate the normal functioning of the kidneys. A reduction in the levels of serum BCCA was observed with the progression of diabetic kidney disease (DKD). These findings in the previous research studies have emphasized the role of branched chain amino acids as a promising future biomarker for the prediction of initiation and progression of the diabetic kidney disease (Liu et al.,2023).

The prevalence of Gestational diabetes mellitus (GDM) is increasing globally and is associated with many adverse neonatal and maternal outcomes and need for neonatal intensive care. It is also associated with a significant risk of later type 2 diabetes in the mother. GDM may lead to obesity and metabolic

syndrome in the offspring (Najmeh Rahimi 2017, Hannah Heath et al., 2022, Huhtala MS et al., 2018). Branched chain amino acids can also serve as markers for increased risk of impaired glucose tolerance during pregnancy or development of type 2 diabetes mellitus after pregnancy. In a longitudinal study, derangements in leucine and isoleucine metabolism were present in the first and second trimester of pregnancy, prior gestational diabetes mellitus (GDM) development (Wang X et al.,2022).The meta-analysis study also indicated a potential role of plasma BCAA for the early diagnosis of GDM. However, metabolomics data showed a decrease in BCAA concentration throughout pregnancy accompanied by no changes in insulin resistance. These observations highlight that higher levels of BCAA alone are not sufficient to trigger insulin resistance and challenge a direct link between blood BCAA content and the risk of insulin signal impairment in pregnant women (Elżbieta Supruniuk et al., 2023).

Serum branched chain amino acids are associated with obesity, insulin resistance and type 2 diabetes mellitus (T2DM) and may be implicated in GDM development starting in early pregnancy (Jiaxi Yang et al.,2023, Gao et al.,2022). The risks of 2 hour changes in BCAAs for GDM women were significant which may provide appropriate information for its prevention and early diagnosis (Gao, B.et al.,2022). A previous study have observed that an increase in fasting and post OGTT glucose levels at 26–28 weeks gestation were significantly associated with mid-childhood individual and total BCAAs concentrations. These findings suggest that elevated maternal glycaemia may have continuous stimulus on programming of amino acid metabolism in offspring and these were associated with abnormal cardiometabolic profiles at mid-childhood (Liu, M.et al.,2023). Serum isoleucine (Ile) in the first trimester was a valuable biomarker for GDM. The combination of serum isoleucine, advanced maternal age and overweight may help in the earlier prediction of GDM (Wang X et al.2022). Plasma BCAAs provides useful information for the prevention and early diagnosis of GDM (Liang Zhao et al.,2019, Adegbenga Bolanle Ademolu et al., 2022).There are many abnormalities in the amino acids metabolism even after optimal control of carbohydrate metabolism during gestational diabetes mellitus (Hawryluk, J et al.,2016). It was suggested that the placental amino acid exchange is altered in GDM pregnancies(Cetin I et al.,2005).

Hypertension is the leading preventable risk factor for cardiovascular disease (CVD).Recent research studies have shown the role of branched chain amino acids (BCAA) in the development of hypertension.Lipoprotein insulin resistance index (LP-IR) is calculated from 6 lipoprotein particle parameters and it has shown strong association with insulin resistance. A new multimarker called the Diabetes Risk Index (DRI) has been developed by integrating lipoprotein insulin resistance index and branched chain amino acids which is associated with an increased risk of type 2 diabetes mellitus (Flores-Guerrero JL et al., 2020, Flores-Guerrero JL et al., 2021). Branched-chain amino acids (BCAA) and related metabolites are more strongly associated with insulin resistance (Newgard CB et al., 2012).

Plasma branched chain amino acids can be used for the assessment of hypertension risk. The increased levels of 3 branched chain amino acids positively correlated with an increased risk of hypertension (Cai S et al., 2024). A prospective research study revealed that high plasma concentrations of branched chain amino acids are associated with an increased risk of newly developed hypertension (Flores-Guerrero JL et al., 2019). The elevated plasma branched chain amino acid is a sign of future development of higher blood pressure in humans and BCAA oxidation lowers vascular resistance(MurashigeD et al.,2022).A research study concluded that the excretion rate of 24-hour urinary branched chain amino acids was closely related to blood pressure in elderly hypertension patients. Recent research studies have shown association between BACC metabolism and blood pressure (Wang F et al.,2021). The branched-chain amino acids are linked to the adverse effects of various cardiovascular diseases(Xu H et al.,2023).

The relationship between dietary intake of branched chain amino acids and blood pressure are controversial in various studies in different populations. One of the study have observed that higher intake of plasma BCAA is clearly related to lower systolic blood pressure (Wang F et al.,2021). Another study also observed higher intakes of BCAA were associated, independently of genetics, with lower insulin resistance, inflammation, blood pressure and adiposity-related metabolites (Jennings A et al.,2016). Contradicting to this, one of the research study have observed that the dietary intake of branched-chain amino acids, in particular valine have been associated with risk of hypertension and increased blood pressure(Liu Y et al.,2022, Mirmiran P et al.,2019,Lin C et al.,2022). Both animal and vegetable protein intake can markedly lower blood pressure(Mirmiran P et al.,2019). The mechanism of action of protein intake on blood pressure is not clearly known and the antihypertensive effect of dietary proteins may be related to the protein source and its amino acid content(Wang F et al.,2021). If dietary pattern includes high fat consumption, branched chain amino acids contributes to development of obesity-associated insulin resistance (Newgard CB et al., 2009).

The relationship between high concentrations of branched chain amino acids and hypertension should be interpretated with caution because their metabolism is complex and complicated influenced by various factors and their plasma levels may not represent the intracellular changes seen in various types of cells (Mahbub MH et al., 2020).There was also a positive relationship between BCAA levels and several markers of energy control (i.e., triacylglycerol, glycerol and leptin) as well as a negative relationship with high-density lipoprotein (HDL) concentration (Elżbieta Supruniuk et al., 2023). Branched chain amino acids exhibited a strong negative correlation with serum HDL. Serum triglycerides were found to have a positive correlation with serum levels of leucine and

valine (Krishnamurthy et al., 2023). Elevated levels of plasma BCAAs are positively associated with triglyceride and HbA1c. They could serve as an effective marker for the assessment of metabolic dyslipidaemia in subjects with type 2 diabetes mellitus (Sankanagoudar S et al., 2022).

Branched chain amino acids serve as a useful biomarker for early detection of insulin resistance and later diabetic risk. Obesity, insulin resistance and hypertension contribute to the development of metabolic syndrome.Plasma branched chain amino acids may serve as potential marker to assess the risk of gestational diabetes mellitus. Diabetes risk index calculated using the parameters lipoprotein and branched chain amino acids may help to assess the risk of type 2 diabetes mellitus.

CONCLUSION:

The metabolism of branched chain amino acids and its link with insulin resistance, hypertension and obesity is a complicated process influenced by various factors and these have to be considered for the clinical interpretation of any changes in its plasma concentration.Branched chain amino acid plays multiple role as a potential novel biomarker in the understanding of the causative mechanism of the development, progression and complications of metabolic syndrome. It may serve as a causative, prognostic as well as a diagnostic marker of abnormal glucose metabolism in different conditions.

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