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Altered Branched Chain Amino Acid Metabolism: Towards a Unifying Cardiometabolic Hypothesis

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Abstract

Purpose of review: Atherosclerotic cardiovascular disease (CVD) and type II diabetes (T2D) share common etiologic pathways that may long precede the development of clinically-evident disease. Early identification of risk markers could support efforts to individualize risk prediction and improve the efficacy of primary prevention, as well as uncover novel therapeutic targets.

Recent findings: Altered metabolism of branched-chain amino acids (BCAAs), and their subsequent accumulation in circulation, may precede the development of insulin resistance and clinically manifest cardiometabolic diseases. BCAAs – the essential amino acids leucine, isoleucine, and valine – likely promote insulin resistance through activation of mammalian target of rapamycin complex 1 (mTORC1). Epidemiologic studies demonstrate robust associations between BCAAs and incident T2D, and Mendelian randomization supports a potentially causal relationship. More recently, there is emerging evidence that BCAAs are also associated with incident atherosclerotic CVD, possibly mediated by the development of T2D.

Summary: In this article, we review the biochemistry of BCAAs, their potential contribution to cardiometabolic risk, the available evidence from molecular epidemiologic studies to date, and, finally, consider future research and clinical directions. Overall, BCAAs represent a promising emerging target for risk stratification and possible intervention, to support efforts to mitigate the burden of cardiometabolic disease in the population.

Keywords

branched-chain amino acids; type 2 diabetes; cardiovascular disease; metabolomics; epidemiology

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INTRODUCTION

The pathogenesis of cardiovascular disease (CVD) is preceded by a prolonged preclinical state that involves dysregulated metabolism, vascular dysfunction, and progressive atherosclerosis. Identifying individuals at elevated CVD risk in the earliest phases of disease pathogenesis could provide opportunities to maximize the effectiveness of primary prevention strategies and reduce the burden of disease in the population.

In search of early markers of CVD risk and potential disease mediators, metabolomics has emerged as a powerful tool to characterize complex states of metabolic dysfunction.(1) Metabolomics involves the integrated profiling of small molecules (<1.0 kDa) in populations, and has been highly effective in identifying novel biomarkers of cardiometabolic disease.(2, 3) Resulting in part from a recent increase in metabolomics research, circulating concentrations of branched-chain amino acids (BCAAs) have been consistently associated with incident T2D as well as other cardiovascular disease risk factors, including excess body weight and obesity, insulin resistance, and T2D.(3) Research to elucidate the role of BCAAs in the development of cardiometabolic disease is ongoing, including efforts to determine whether there is a causal relationship amenable to intervention. In this review, we consider the biochemistry of BCAAs, their potential contribution to cardiometabolic risk, review the available evidence from molecular epidemiologic studies to date, and, finally, consider future directions.

BRANCHED-CHAIN AMINO ACIDS

Leucine, isoleucine, and valine, collectively BCAAs, are essential amino acids that contribute to protein synthesis and perform a wide range of well-characterized metabolic and physiologic functions.(4) BCAAs are ubiquitous throughout the diet, available from a variety of both vegetable and animal protein sources; however, determinants of between- and within-person variability in circulating BCAA concentrations are largely unknown. Short-term feeding trials in patients with chronic illness or healthy athletes demonstrate that increases in BCAA intake, either from BCAA-enriched diets or supplements, results in modest, temporary rises in plasma BCAA concentrations.(5–8) However, the long-term effects of BCAA intake and supplementation on circulating BCAA concentrations among more generalizable populations are lacking.

Although BCAAs are essential amino acids derived solely from the diet, correlations between diet and circulating BCAAs in the Nurses' Health Study and Health Professionals Follow-up Study longitudinal cohorts appear at most modest (r~0.2), suggesting factors other than dietary intake may determine plasma concentrations of BCAAs.(9, 10) Further, circulating concentrations of BCAAs in plasma, serum, and urine, are strongly associated with poor cardiometabolic health, as reviewed below, while the magnitudes of the associations for dietary intakes of BCAAs with the same endpoints are lacking(11) or marginal(9, 12). Recently, we compared the dietary intakes of BCAAs and plasma concentrations of BCAAs in high risk women, and observed that women with elevated plasma levels, rather than dietary BCAAs alone, experienced a greater risk of incident T2D.

(10) These findings suggest that underlying catabolic defects in BCAAs metabolism, resulting in elevated BCAA circulating concentrations, may be the relevant cardiometabolic risk factor, rather than the amount of dietary BCAA intake *per se* (Figure 1).

Identifying the determinants of impaired BCAA catabolism or elevated circulating BCAA concentrations are critical to understanding the role of BCAAs in cardiometabolic health and disease. Excess body weight and central obesity are positively correlated with circulating BCAAs across a number of disease-free study populations, implicating excess adiposity as an important determinant of circulating BCAA concentrations.(13–16) (17–19) Genetics may also influence individuals' underlying BCAA metabolism, and, in turn, circulating BCAA levels, although likely to a small extent. A recent genome-wide association study (GWAS) identified 5 genetic regions significantly associated with higher plasma BCAAs, explaining 7.5%, 6.3%, and 5.3% of the heritability of isoleucine, leucine, and valine metabolites, respectively.(20) Decreased BCAA uptake by muscle and other tissue,(21) muscle breakdown or cachexia,(22) and lower branched-chain keto acid dehydrogenase (BCKD) enzyme activity(23) have also been identified as conditions resulting in elevated BCAA concentrations.(24) Other potential modifiable determinants of variability in concentrations of BCAAs, such as level of physical activity, overall dietary quality or other dietary factors, and the microbiome have not yet been fully elucidated, warranting further research.

ELEVATED BCAA CONCENTRATIONS AS A FEATURE OF POOR CARDIOMETABOLIC HEALTH

Accumulating evidence implicates dysregulated BCAA metabolism in the pathogenesis of T2D and CVD. Of the thousands of metabolites in circulation, BCAAs have been consistently identified across study populations, follow-up durations, and methods of metabolomic profiling, for their strong positive relationship with impaired glucose metabolism,(25) insulin resistance,(15, 26) and incident T2D,(3).These observations support the hypothesis that BCAA metabolism may be implicated early in the development of insulin resistance and eventual T2D.(27–29) Evidence from human and animal studies demonstrates that the controlled introduction of dietary amino acids, including BCAAs, has the ability to impair insulin action and signaling in skeletal muscle through upregulation of the mTOR pathway.(30–35) Further, small randomized trials of metformin, an insulin-sensitizing drug, did not demonstrate an effect on BCAA levels vs. placebo.(36, 37) These findings suggest that alterations in BCAAs metabolism may occur upstream of insulin resistance, rather than as a downstream consequence.

Importantly, recent evidence from Mendelian randomization analyses support a causal role for BCAA metabolism in T2D risk, wherein genetic determinants of elevated circulating BCAA levels were positively associated with risk of T2D.(20, 38) Further, these genetic predictors were related to impaired BCKD) activation, the rate-limiting step in BCAA break-down.

While the link between BCAAs with T2D is well-recognized, prospective analyses of circulating BCAA metabolites in relation to incident CVD events are sparse and/or

inconsistent. Several prospective metabolome-wide studies of incident coronary heart disease(39, 40), coronary artery disease(41–43), and myocardial infarction (MI),(43) have failed to identify BCAAs as significantly associated with CVD, possibly owing to limited statistical power following adjustment for multiple hypothesis testing. However, in a candidate approach, the PREvención con DIeta MEDiterránea (PREDIMED) Mediterranean diet trial prospectively evaluated baseline plasma BCAA concentrations in relation to incident CVD among 970 men and women at high risk.(44) In BMI-adjusted models comparing the 4th and 1st quartiles, isoleucine, leucine, and valine baseline plasma concentrations were significantly associated with 2.9, 2.2, and 1.9-fold greater risks of incident cardiovascular events (primarily stroke), respectively.

We recently analyzed BCAAs in relations to CVD risk among 27,041 women in the Women's Health Study (WHS) prospective cohort who were free of CVD and cancer at the baseline blood collection.(45) We confirmed 2,207 first CVD events (MI, stroke, coronary revascularization) over an average 18.6 follow-up years. With multivariable models adjusting for age, BMI, and other established CVD risk factors, we observed that plasma concentrations of total BCAAs were positively associated with incident CVD, as shown in Figure 2.(adjusted hazard ratio [HR] per standard deviation [SD] increment=1.13; confidence interval (CI)=1.08 to 1.18). This magnitude of risk was comparable to the association between LDL cholesterol and CVD risk (per SD HR=1.12, CI=1.07 to 1.17). In WHS, BCAAs were associated with coronary events (MI: HR=1.16, CI=1.06 to 1.26; revascularization: HR=1.17, CI=1.11 to 1.25), but not significantly with total stroke (HR=1.07, CI=0.99 to 1.15). Notably, the relationship between BCAA concentrations and CVD risk was greater among women with T2D diagnosed prior to CVD (HR=1.20, CI=1.08 to 1.32), vs. women without T2D (HR=1.08, CI=1.03 to 1.14), and in those women the association with stroke as well as MI was also significant. Adjusting for LDL-C, an established CVD risk factor, did not attenuate these findings; however, adjusting for HbA1c and insulin resistance eliminated the associations of BCAAs with CVD. In a separate cross-sectional analysis, plasma BCAAs were positively correlated with carotid intima-media thickness (cIMT) among adult subjects with HbA1c values ≥5.6%, while no correlation between BCAAs and cIMT persisted among the subgroup of individuals with Hba1c<5.6%. (46) Thus, BCAAs may confer an elevated risk of CVD through insulin resistance- and T2D-related atherosclerosis risk.

BCAAs AND HEART FAILURE

Metabolic reprogramming is one of the hallmarks of heart failure. Alternations in myocardial substrate utilization plays can influence overall myocardial ATP generation, and affect cardiac function.(47) Over the past few years, accumulating evidence suggests that the suppression of BCAA catabolic gene expression along with concomitant tissue accumulation of branched-chain α-keto acids occurs in experimental and clinical cardiac failure, and that this may be mediated upstream through aberrant changes in Krüppel-like factor 15.(48) The accumulation of these branched-chain α-keto acids have been linked to heart failure through a potential direct effect to inhibit respiration and promote an increase in the release of potent reactive oxygen species, such as, superoxide, within the mitochondria. Intriguingly, the heart failure benefits of some of the newer antihyperglycemic agents, such

as empagliflozin, has been suggested to be mediated through improving BCAA catabolism.(49) More recently, research in mice have demonstrated that impaired BCAA catabolism resulting in a buildup of BCAA's served to impair glucose metabolism and increased the susceptibility of the heart to ischemia. Strikingly, approaches that augmented BCAA catabolism had beneficial effects on the myocardium.(50)

BCAAS AS MODIFIABLE TARGETS FOR PRIMARY PREVENTION

BMI, diet, and physical activity contribute substantially to the development of poor cardiometabolic health, and play pivotal roles in primary prevention strategies for T2Dand CVD.(51–53) A recent rat model demonstrated that up-regulating branched-chain ketoacid dehydrogenase (BCKDH), a critical step in BCAA catabolism, lowered circulating BCAA concentrations and led to improvements in glucose tolerance, independent of weight loss.(54) However, the identification of modifiable risk factors capable of modifying rates of BCAA catabolism and subsequent circulating BCAA concentrations in humans is sparse. Identifying improved BCAA metabolism, as reflected by lowered BCAA concentrations, as a relevant mediator underlying the impact of lifestyle on cardiometabolic health would allow for more efficient therapeutic strategies and the identification of high risk subgroups years prior to disease onset.

Two weight loss trials, POUNDS LOST and DIRECT, observed significant correlations between BCAA metabolite levels and weight loss between baseline and 2 years.(55) Further, small prospective studies of subjects undergoing bariatric weight-loss surgery found correlations between post-operative weight loss and BCAA levels, with one study reporting a significant 20% reduction in plasma BCAAs concurrent with 20% body weight loss.(56, 57) Collectively, these evidence support the potential modifiability of BCAA metabolism with weight loss and their potential as efficient targets for intervention and primary prevention. Another diet-induced weight loss trial with 7.4% average percent body weight loss did not observe significant reductions in individual or total BCAA concentrations. Lower valine concentrations, however, were independently correlated with improved HOMA-IR, a metric of insulin resistance, at 6 months follow-up.(58)

Evidence for effects of diet and physical activity, independent of weight loss, on circulating BCAA concentrations is mixed. Although BCAAs are essential amino acids derived solely from diet, short-term manipulations of dietary BCAA intake have resulted in only modest changes in circulating BCAA concentrations.(8, 59) One study in diet-induced obese mice reported that dramatically reducing dietary BCAAs by 66% led to reductions in weight and restored measures of glucose homeostasis, although results were not independent of unintended increases in the animals' energy expenditure.(60) The PREDIEMD Mediterranean diet trial reported a significant reduction in plasma BCAAs between baseline and 1-year follow-up with the healthful Mediterranean dietary intervention, and no change in the low-fat control group.(61) Further, increases in isoleucine between baseline and 1 year, but not valine or leucine, was associated with a significant nearly 2-fold greater T2D risk compared with no change in isoleucine. Baseline BCAA concentrations were also associated with a significantly higher risk of incident CVD in the control group, but this association was mitigated in the Mediterranean diet intervention groups.(44) In contrast, the

Diabetes Prevention Program, which observed significant effects of an intensive diet and lifestyle intervention on reductions in T2D incidence, did not observe significant changes in BCAAs between baseline and 2 years follow-up.(62)

A small cross-sectional analysis of physical activity in Chinese adults (N=277) found that BCAAs had the strongest association with physical activity among the ~300 metabolites evaluated, with lower BCAA levels associated with greater usual physical activity.(63) An analysis of twin studies compared a number of cardiometabolic markers, including lipids and BCAAs for active vs. inactive twins, observing significantly lower isoleucine levels among the regularly active individuals.(64) Finally, an aerobic exercise training intervention induced greater plasma BCAA turnover and increased insulin sensitivity among overweight trained subjects vs. overweight untrained subjects over 6 months.(65) Physical activity may increase BCAA degradation through increased BCAA metabolism-related gene expression in muscle and adipose tissue.(66) Overall, some lifestyle factors, including a Mediterranean-style dietary pattern and physical activity, may confer health benefits through improved BCAA metabolism. Although promising, limitations of the sparse literature include small sample size, cross-sectional study design, and poor control for potential confounders. Additional research is needed to identify and confirm which lifestyle and therapeutic interventions would effectively increase BCAA catabolism and reduce circulating BCAAs, and whether such improvements would appreciably modify risks of subsequent cardiometabolic disease.

CONCLUSIONS: FUTURE DIRECTIONS FOR BCAAS IN CARDIOVASCULAR DISEASE RESEARCH AND PREVENTION

BCAAs have been consistently observed as strongly associated with elevated T2D risk, and compelling experimental evidence and genetic epidemiologic studies suggest a potentially causal role of impaired BCAA metabolism in the development of insulin resistance and T2D.(20, 38, 54) However, their relationship with CVD is less consistent, but emerges particularly in those with intermediate T2D. Thus, impaired BCAA metabolism may represent a pathway consistent with the “common soil hypothesis”; a shared pathology predisposing to both cardiometabolic conditions.(67) Understanding where these potential common risk pathways converge and diverge along the road to CVD and T2D risk has important implications for how risk is identified and mitigated in vulnerable populations.

To date, little research has been undertaken to identify upstream determinants of dysregulated BCAA metabolism or elevated circulating BCAA levels. Future efforts to identify modifiable contributors to circulating BCAA concentrations, beyond dietary BCAAs or supplements, may optimize T2D prevention strategies, generate effective interventions for individuals at particularly high T2D risk, and lead to novel targeted therapeutics.

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KEY POINTS:

- Altered metabolism of branched-chain amino acids (BCAAs), and their subsequent accumulation in circulation, may precede the development of insulin resistance and cardiovascular disease.
- While the link between BCAAs with T2D is well-recognized, prospective analyses of circulating BCAA metabolites in relation to incident CVD events are sparse and/or inconsistent.
- BCAAs may confer an elevated risk of CVD through insulin resistance and T2D-related atherosclerosis.
- Identifying the determinants of impaired BCAA catabolism or elevated circulating BCAA concentrations are critical to understanding the role of BCAAs in cardiometabolic health and disease.

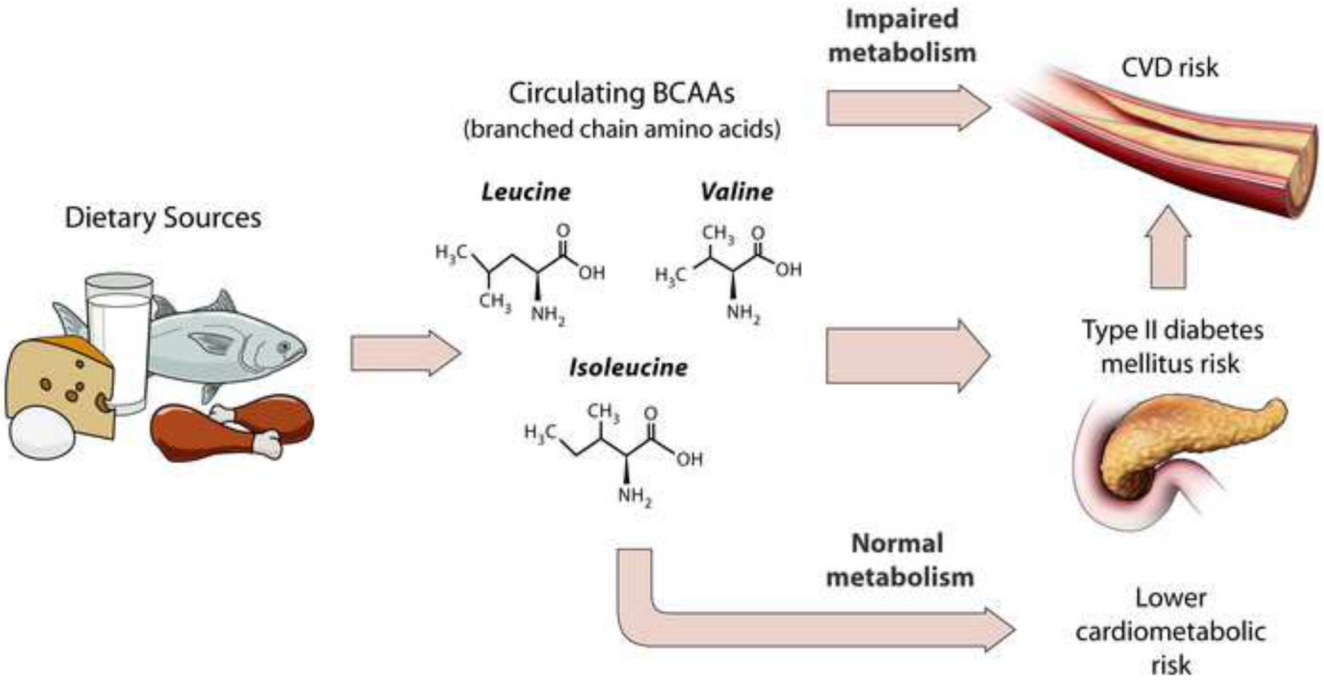

FIGURE 1.

Impaired metabolism of branched-chain amino acids, elevated circulating concentrations, and subsequent risks of type 2 diabetes and cardiovascular disease.

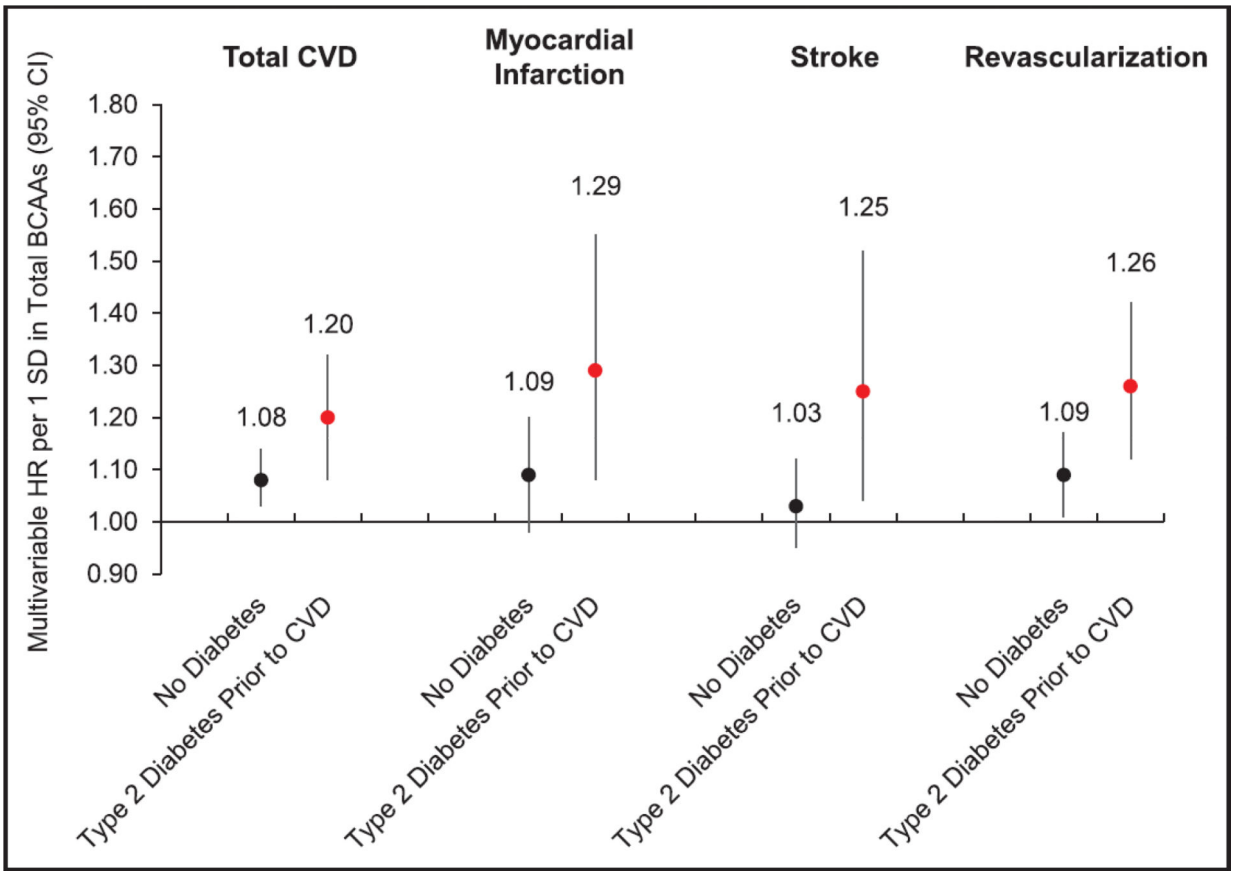

FIGURE 2. Prospective association between baseline circulating total branched-chain amino acids (BCAAs) in relation to incident total cardiovascular disease (CVD), myocardial infarction (Ml), stroke, and revascularization risk in 27401 US women, according to type 2 diabetes mellitus diagnosis before CVD end point.

Multivariable-adjusted model includes the following: age (continuous), randomized treatment assignments (aspirin, beta- carotene, and vitamin E), fasting status at blood draw, menopausal status (pre, post, uncertain, and missing), current hormone therapy use, family history of Ml, White race/ethnicity, smoking status (never, past, current <15 c/d, current 15+ c/d). Alternative Healthy Eating Index (AHEl) diet quality score (quintiles), alcohol intake (4 categories), total physical activity metabolic equivalent of tasks (MET)-h/wk (quintiles), history of high cholesterol, history of hypertension, and body mass index (10 categories). A values for interaction: total CVD, P=0.036; Ml, P=0.059; stroke, P=0.066; and revascularization, P=0.019. Cl indicates confidence interval; and HR, hazard ratio.