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Restricting branched-chain amino acids: an approach to improve metabolic health

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Obesity and related metabolic conditions such as type 2 diabetes mellitus (T2DM) are increasing in prevalence in the United States. While restricting caloric intake or increasing caloric expenditure has been shown to be effective in achieving weight loss, the effects are difficult to maintain without major lifestyle changes. Many people who attempt to lose weight through these means regain the weight lost. New weight loss approaches which are easier to maintain long term are needed.

Increased levels of branched-chain amino acids (BCAAs) have been correlated with obesity, insulin resistance and T2DM. While some research has shown beneficial effects of high BCAA consumption, the correlation with insulin resistance suggests that high levels of BCAAs may in fact be detrimental to metabolic health. The seemingly contradictory evidence of the effects of high BCAA levels leaves an important question to be addressed regarding the role of BCAAs in metabolic disorders such as T2DM. A mechanism for the role of BCAAs in the development of insulin resistance has been proposed involving the activation of mammalian target of rapamycin complex 1 (mTORC1). This proposed mechanism suggests that activation of mTORC1 causes insulin receptor substrate 1 (IRS-1) serine phosphorylation, which may result in insulin resistance. However, controversy over the validity of this mechanism exists. Also, impairment of BCAA metabolism in insulin resistant conditions leads to accumulation of BCAAs which may contribute to mitochondrial dysfunction and beta cell apoptosis. Thus, further research is necessary to understand the role that BCAAs play in insulin resistance (Yoon, 2016).

Fibroblast growth factor 21 (FGF21) is a hormone secreted from the liver and other tissues, and acts on target organs including adipose tissue, pancreas, hypothalamus and liver. It is regulated in response to stressors such as fasting, malnutrition, high-fat diet, obesity, amino-acid deprivation, mitochondrial stress, cold temperature and exercise to maintain energy homeostasis. It has multiple effects on energy homeostasis, including browning of adipose tissue, thermogenesis, increasing lipolysis, increasing glucose uptake, increasing ketogenesis, increasing bone loss, increasing fatty acid oxidation and decreasing fatty acid synthesis. Increased levels of FGF21 are associated with obesity in an attempt to restore metabolic homeostasis. Further increasing the levels of FGF21 has been shown to improve metabolic parameters including weight loss and insulin sensitivity, suggesting that it may be an effective target for the prevention and treatment of T2DM. Some evidence exists showing a link between BCAA restriction and the induction of FGF21 expression, leading to increased lipolysis and decreased lipogenesis (Kim & Lee, 2014).

A recent study conducted by Cummings *et al.* (2018), and published in *The Journal of Physiology*, supports the argument that BCAAs have an important role in the development of insulin resistance, and shows that dietary BCAA restriction can improve insulin sensitivity and weight loss, possibly through FGF21-mediated effects. Cummings *et al.* used a mouse model to demonstrate the effects of a diet low in BCAAs on weight loss and restoring metabolism. Their findings demonstrated that a diet low in BCAAs or low in total amino acids (AAs) promotes energy expenditure, despite isocaloric diets and similar activity levels across all test groups.

Several cohorts of mice were used. The first was placed on a western diet (WD) to induce obesity, then individuals were switched to a normal diet, normal diet with low BCAAs, or normal diet with low AAs. In the second cohort, obesity was induced via a WD, but mice remained on a WD with low BCAAs or low AAs.

A low BCAA diet showed significant effects on hepatic steatosis. Mice consuming a low BCAA diet showed decreased liver lipid droplet size, despite remaining on a WD. Effects on hepatic steatosis in low AA mice were much less dramatic. Insulin resistance improved in both the low BCAA group and the low AA group. Both groups showed improved glucose tolerance, even above control mice never exposed to a WD.

Additionally, both altered protein composition diets showed improved body composition, with thinner dermal white adipose tissue and decreased overall adiposity. The researchers found that the respiratory exchange ratio of mice on a low BCAA or low AA diet was indistinguishable between the two groups, but significantly increased over the WD control mice. Spontaneous activity levels were the same across all groups. Despite this, mice on a low BCAA or low AA diet were found to have significantly greater energy expenditure. Cummings *et al.* (2018) suggested that this effect may in part be attributed to the activation of brown adipose tissue (BAT) via FGF21.

In the third cohort of mice used, the researchers found that FGF21 was significantly increased in WD low BCAA and low AA mice 12 days after the diets were switched. FGF21 is known to increase activation of BAT and promote browning of white adipose tissue (WAT). However, no changes in browning or induction of Uncoupling Protein 1 (UCP1) were observed in WAT. BAT may have been activated by non-traditional methods, which may explain the increase in energy expenditure observed. It is important to note that the induction of FGF21 was only observed in mice on a low BCAA or low AA diet in combination with a WD.

In this study, diets low in BCAAs, as well as diets low in total AAs, effectively induced weight loss as well as increased insulin sensitivity and blood glucose tolerance. Interestingly, nearly identical phenotypical changes were seen in both low BCAA and low AA diets. Although both diets have been shown to cause similar effects, previous research has shown that these changes are due to different mechanisms (Fontana *et al.* 2016), which was supported by this study. Because most of the weight loss in the mice fed a low BCAA or low AA diet occurred during the first 3 weeks of the study, Cummings *et al.* (2018) studied the third cohort of mice and measured FGF21 and energy expenditure after just

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12 days. A surprising finding was that FGF21 expression after 12 days was actually higher in mice consuming a diet low in BCAAs than in the mice consuming a diet low in AAs. This finding suggests that altering amino acid composition of a diet may be just as effective as restricting total protein in restoring metabolic health, although the mechanisms appear to be different.

An important side effect that should be noted in this study is that, by switching mice from a WD to a normal caloric diet low in BCAAs or low in AAs, a significant loss in lean mass was observed. In the first model, a protein reduction of 78% was used, resulting in approximately 20% loss of lean mass, in addition to large amounts of fat mass. In the second model, a more physiologically relevant protein reduction of 67% was used, which successfully mitigated the reduction in lean mass. Should this study be applied to human subjects, care must be taken to avoid lean mass loss due to protein restriction.

Further research should investigate whether these improvements in metabolic health will occur in humans in the same way that they occur in mice. Mice have a much higher ratio of BAT to WAT than humans do. Because FGF21 activates BAT, which contributes to increased energy expenditure and weight loss, it is important to determine whether humans could have the same drastic results in weight loss as the mice did. Because of this difference, the most significant contribution of this study may be the findings on insulin resistance and glucose tolerance. Smith *et al.* (2016) showed that insulin resistance is not improved in humans when diets include high protein levels, even when accompanied by weight loss. The study by Cummings *et al.* (2018) supports these findings in that low AA and low BCAA diets improved insulin resistance and blood glucose tolerance. These changes may be partially independent of weight loss.

These findings suggest that reducing BCAAs may be an important factor in improving metabolic health. If the results of this study translate to humans, showing that lowering dietary BCAAs improves insulin sensitivity and contributes to weight loss, this may open the door for an inexpensive and sustainable dietary intervention for patients with T2DM. This study provides some evidence towards a link between BCAAs and FGF21. Further research should address the effects of BCAA restriction on FGF21 expression in humans. This may include investigating the capacity to activate brown adipose tissue and cause the beiging of white adipose tissue, as well as effects on mitochondrial function.

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Additional information

Competing interests

None declared.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.