Assessment of Branched-Chain Amino Acid Status and Potential for Biomarkers

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ABSTRACT BCAAs are not synthesized in the body in humans, but they are crucial in protein and neurotransmitter synthesis. The protein anabolic role of BCAAs seems to be mediated not only by their important role as a promoter of the translation process (and possibly acting at the transcription level) but also by inhibition of protein degradation. Leucine may play a critical role in these signaling pathways. Supplementation with BCAAs spares lean body mass during weight loss, promotes wound healing, may decrease muscle wasting with aging, and may have beneficial effects in renal and liver disease. BCAA supplementation is extensively used in the athletic field with the assumption of improved performance and muscle mass. Measuring serum BCAAs has limited clinical utility beyond the controlled setting because levels are affected by a variety of clinical states, and optimal levels in these scenarios have not been completely elucidated. We discuss the effects diet, hormones, stress, aging, and renal or liver dysfunction have on BCAA levels and how understanding the biological effects of BCAAs may help to develop biomarkers of BCAA status. We also discuss potential biomarkers of BCAA status. J. Nutr. 136: 324S–330S, 2006.

KEY WORDS: • branched-chain amino acids • hormones • protein synthesis • protein degradation

BCAAs consist of leucine, isoleucine, and valine. They are considered essential because they cannot be synthesized de novo and must be obtained from the diet. They are necessary for protein and neurotransmitter synthesis. BCAAs also are important sources of nitrogen for synthesis of nonessential amino acids, such as glutamine and alanine. There is increasing evidence of their pivotal role in regulating the anabolic process involving both protein synthesis and degradation. Furthermore, BCAAs have therapeutic potential because they are reported to spare lean body mass during weight loss (1), promote wound healing (2), promote muscle protein anabolism in muscle wasting with aging (3), and have beneficial effects in the setting of renal and liver disease (4,5). BCAAs are also extensively used by athletes based on an assumption that they promote muscle anabolism. BCAAs alone have an advantage because there is minimal addition of calories, no stimulation of gluconeogenesis, and no increase in glomerular filtration rate that is reported to occur with other amino acids, such as alanine, or following a high protein diet. They are useful in liver failure because they are mostly metabolized in muscle as opposed to liver. However, there are no valid measures to determine deficiency, adequacy, or excess of BCAAs that can guide their use in therapy. Ideally, biomarkers of BCAA status should convey the adequacy of BCAAs to maintain the vital functions of protein synthesis and breakdown. In this article, we will discuss the limitations of various options and the potential for future biomarkers.

Can we use BCAA levels in blood as markers of their status?

Although using serum BCAAs would conceptually be appealing as a biomarker, there are limitations. In a controlled laboratory setting, serum/plasma BCAAs are very useful as one of many tools to assess protein degradation/protein synthesis. The basic pharmacokinetics, i.e., plasma clearance, volumes of distribution, and half-lives of individual amino acids (AAAs) have been described (6). In the fasted state, the only source of BCAAs is appearance from protein degradation, which is a key process for maintenance of quality of proteins and repair process of tissues. BCAA levels in the postabsorptive state remain within a small range in a healthy population. It is logical to think that BCAA or essential AA oxidation increases when the levels of these AAs exceed the requirement. In fact, the 24-h
pattern in leucine oxidation is paralleled by plasma leucine concentrations in the fed state (7). However, it may be more reliable to interpret BCAA levels in steady-state conditions. For example, during infusion with continuous parenteral nutrition, plasma levels can reach a plateau in 3 h, and there is a correlation between plasma enrichment and rate of perfusion of AAs (8).

The difficulty with measuring BCAA levels is that they can increase with enhanced protein degradation but do not necessarily indicate excess. They can also decrease due to a variety of factors and do not necessarily indicate deficiency (9). This will be further discussed in detail. Another problem is that serum BCAAs usually refer to levels in peripheral venous blood. The AA profile in venous blood can be different from arterial blood (10); therefore, this must be considered in interpreting measurements. Also, plasma vs. whole-blood AAs are not always the same. Whole-blood AAs represent both plasma and intracellular AAs in blood cells. For example, it has been found that whole-blood concentrations of certain AAs, like aspartate, are severalfold higher in whole blood than in plasma (11). This is because some AAs are highly concentrated in red blood cells, especially in situations such as exercise (10). It remains to be determined whether the relationships between plasma and tissue BCAA levels are constant in all conditions and similar in all tissues. In fact, based on isotope studies, it appears that these relationships may be altered in muscle even in similar physiological states (9). The function of BCAAs is likely to be determined more by intracellular concentrations than plasma concentrations. Therefore, future studies must consider direct measurements of tissue BCAA levels or markers of them to determine true status.

Nitrogen balance may be a better reflection of the overall anabolic vs. catabolic state of body proteins. Nitrogen balance if properly done is a good measure of adequacy of protein intake or AA intake. However, the measurement of nitrogen balance is a rather difficult and time-consuming process (11) and therefore is not practical in population studies and in many clinical settings even in hospitalized patients. It provides no answer regarding adequacy in specific tissues or certain AAs and therefore is not a good surrogate for BCAA status.

Whole-body protein turnover and leucine oxidation can be used to assess adequacy of AA (specific) requirements. In one study, daily protein oxidation was the same when estimated from leucine oxidation or nitrogen excretion. Thus, the tracer-balance concept is valid, and reliable predictions of total daily leucine oxidation and whole-body leucine balance can be obtained from short-term measurements of leucine oxidation during fasted and fed states (12). However, measurement of overall AA oxidation may not distinguish protein accretion at the specific tissue level because BCAAs are mainly transported into the muscle and oxidized in liver. Muscle protein synthesis can specifically be analyzed, however, by isotope-based approaches and muscle myofibrillar degradation from arterio-venous balance or isotope-based measurement of efflux of 3-methylhistidine across the muscle bed. The roles of other organs in the metabolism of BCAAs have not been fully assessed in humans.

Metabolism of BCAA

BCAAs, just like any other essential AA, undergo acylation of transfer RNA for protein synthesis, and their only other fate is catabolism. The process of catabolism is unique for BCAAs. The important step in BCAA catabolism in the fasted state is primarily by peripheral tissues (particularly muscle) rather than liver in the following three steps: transamination, oxidative decarboxylation, and dehydration.

The dehydrogenation products of leucine (acetoacetate and acetyl coenzyme A) are ketogenic, whereas that of valine (succinyl coenzyme A) is glucogenic. The dehydrogenation products of isoleucine (acetyl coenzyme A and succinyl coenzyme A) are ketogenic and glucogenic. Succinyl coenzyme A is also a precursor of porphyrins (13). When leucine levels fall below normal, branched-chain ketoacid dehydrogenase is inhibited. Conversely, excess leucine can activate this branched-chain ketoacid dehydrogenase complex. Several factors, especially alterations in physiological state, hormones, and various substrates, can affect BCAA oxidation.

Biological effects of BCAAs

While searching for potential markers of BCAAs, it is important to understand the various biological functions of BCAAs.

The effect of BCAAs on AA levels and protein synthesis/protein degradation. Whereas in vitro studies have shown that leucine can stimulate the signaling pathway of translation (14,15) and specifically muscle protein synthesis (16,17), most in vivo studies in humans have shown that infusion of BCAAs results in decreased protein degradation with little or no effect on protein synthesis when given without other essential AAs (18).

These conflicting results regarding protein synthesis have been explained by a reduced level of substrate of other AAs being the limiting factor toward protein synthesis. BCAAs can affect other AA levels by reducing AA efflux from muscle due to inhibition of muscle protein degradation (19,20; this in the absence of insulin stimulation) (Table 1, Fig. 1). Excess leucine in particular (acting through the branched-chain α-ketoacid dehydrogenase complex) decreases valine and isoleucine, which may then compromise protein synthesis in animal models (21).

Differences in whole-body vs. skeletal muscle protein degradation can be explained by the regional contributions of different tissues to whole-body protein degradation. Using leucine and phenylalanine tracers, degradation was found to be greater than synthesis in the kidney and leg but equivalent in the splanchnic region in the postabsorptive state (22). Also, the dehydrogenation products of leucine (acetoacetate and acetyl coenzyme A) are ketogenic, whereas that of valine (succinyl coenzyme A) is glucogenic. The dehydrogenation products of isoleucine (acetyl coenzyme A and succinyl coenzyme A) are ketogenic and glucogenic. Succinyl coenzyme A is also a precursor of porphyrins (13). When leucine levels fall below normal, branched-chain ketoacid dehydrogenase is inhibited. Conversely, excess leucine can activate this branched-chain ketoacid dehydrogenase complex. Several factors, especially alterations in physiological state, hormones, and various substrates, can affect BCAA oxidation.

### Table 1

<table>
<thead>
<tr>
<th>AAs</th>
<th>Saline (μmol/L)</th>
<th>Leucine (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>223 ± 21</td>
<td>200 ± 24</td>
</tr>
<tr>
<td>Arginine</td>
<td>62 ± 10</td>
<td>58 ± 4</td>
</tr>
<tr>
<td>Glycine</td>
<td>143 ± 11</td>
<td>132 ± 14</td>
</tr>
<tr>
<td>Glutamine</td>
<td>381 ± 14</td>
<td>448 ± 38</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>123 ± 18</td>
<td>102 ± 11</td>
</tr>
<tr>
<td>Histidine</td>
<td>143 ± 9</td>
<td>130 ± 7</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>47 ± 3</td>
<td>22 ± 2*</td>
</tr>
<tr>
<td>Leucine</td>
<td>112 ± 6</td>
<td>480 ± 27*</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>43 ± 3</td>
<td>32 ± 2*</td>
</tr>
<tr>
<td>Serine</td>
<td>76 ± 5</td>
<td>60 ± 6*</td>
</tr>
<tr>
<td>Threonine</td>
<td>79 ± 7</td>
<td>59 ± 6*</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>35 ± 4</td>
<td>22 ± 5*</td>
</tr>
<tr>
<td>Valine</td>
<td>134 ± 9</td>
<td>74 ± 5*</td>
</tr>
</tbody>
</table>

Values are means of three points at 30-min intervals over 90 min ± SE; n = 6. *P < 0.05–0.001 leucine vs. saline. Adapted from Nair et al. (20).
because muscle is where BCAA catabolism mainly occurs, BCAA infusion may have different effects on different tissues. Protein degradation was more markedly suppressed when a nonleucine tracer was used (18,20) as compared with a leucine tracer during the unlabeled leucine infusion. This may be related to the changes in pool size of free leucine in different compartments.

**BCAAs in the fasting/starvation state.** In the first few days, glucose is used as the source of fuel for the brain. The liver uses glycogen degradation in the first 10 to 18 h and then increases gluconeogenesis (13). Muscle protein degradation provides AAAs that are used by liver for gluconeogenesis (alanine and glutamine being the most important), and BCAAs are sources of nitrogen for muscle synthesis of gluconeogenic AAs, such as alanine and glutamine. This has been demonstrated in short-term fasting studies, i.e., 1–3 d during which whole-body and muscle protein degradation and leucine oxidation increased (23). Levels of BCAAs rise in the fasting state in parallel with increased protein degradation. (Fig. 2). After several weeks, the rate of muscle protein degradation decreases owing to a decline in the need for glucose as a fuel for the brain. The brain switches to ketones as a source of its energy needs (24,25). As a result, BCAA levels also decline.

Interestingly, it has been shown that β-hydroxybutyrate promotes muscle protein synthesis, although how ketones promote muscle protein synthesis remains unclear (26). Also, vitamin B-6, thiamine, riboflavin, and lipoic acid are necessary for catabolism of BCAAs, so a nutritional deficiency from prolonged starvation may affect BCAA metabolism.

**BCAAs in the fed state.** AA infusion promotes protein synthesis in muscle and splanchnic tissues and inhibits protein degradation mostly in muscle (27). Excess intake of BCAAs will initially result in increased plasma levels, but BCAAs will then be oxidized and form ammonia because there is no storage molecule to control concentrations of BCAAs. The effects of other macronutrients on BCAA levels are less clear. Lipid infusion exhibited a hypoaminoacidemic effect during fasting and following euglycemic and hyperglycemic hyperinsulinemia but did not modify AA concentration in hyperglycemia with basal insulin (28). Long-chain fatty acids have been demonstrated in vitro and in vivo to have protein-sparing effects (29,30). They inhibit endogenous protein degradation and may suppress leucine oxidation in the whole body but do not affect protein synthesis. Medium-chain fatty acids have been shown to increase BCAA oxidation in some studies (29,31) but not in others (32). Carbohydrate effects are even more controversial because they have effects on insulin and glucagon, which in turn have effects on protein synthesis and degradation. In human studies, there is no effect on protein degradation or leucine oxidation when intravenous carbohydrates are given (33,34), but there is some evidence that hypercaloric refeeding with high-carbohydrate diets may increase protein turnover (35).

**BCAAs and hormones.** The key hormones that regulate blood levels of glucose, insulin, and glucagon also have a profound effect on BCAAs.

Infusion of insulin has been shown to decrease BCAA levels compared to controls. Insulin’s anabolic effect is mainly on muscle, where it inhibits protein breakdown, enhances amino acid–induced protein synthesis, and reduces leucine transamination (Fig. 3). Together, insulin and AAAs led to suppression of protein degradation and stimulation of protein synthesis. The maximal effect of insulin combined with AAs is on muscle (27).

Insulin decreases leucine transamination (an important biochemical process for nitrogen transfer between AAs and across the organs), whereas a higher percentage of ketoisocaproate (immediate precursor of oxidation) transaminated was oxidized (36). This occurs in a dose-dependent manner, with the magnitude of effect being greater on skeletal muscle than on the splanchnic bed (37). Part of insulin’s effect on leucine transamination is secondary to the reduction in BCAAs.

Whereas insulin is a key hormone in regulating muscle protein degradation, BCAAs have a more pronounced effect on protein degradation and protein synthesis in splanchnic bed (27). This may reflect the postprandial state. Because splanchnic tissues may account for a significant fraction of body protein synthesis and degradation, if there is variable hepatic protein turnover, this may affect whole-body responses. BCAAs may also have an effect on insulin levels. Leucine and isoleucine have been shown to stimulate insulin release (38). Interestingly, valine had little effect on insulin, but equal amounts of the individual AAs were given, and it is known that plasma and tissue concentration vary by individual AA (39). Moreover, the stimulatory effect of leucine and isoleucine on insulin secretion is less in adults and older people than in the young.

Glucagon, glucocorticoids, and catecholamines are considered catabolic hormones associated with clinically stressful situations. All of them affect protein degradation with an impact on net protein balance (40). In humans, glucagon has been well established to affect BCAA metabolism (41) (Fig. 4). Glucagon has been shown to increase oxidation of leucine with slight enhancement of leucine flux during insulin deficiency (Fig. 5). In dogs, although hyperglucagonemia did not seem to affect whole-body protein degradation or synthesis, arterial plasma AAs (but not BCAAs) did decrease significantly (42). The BCAAs are also poor secretagogues of glucagon, unlike glucogenic AAs, such as alanine, arginine, etc. Leucine and isoleucine may actually inhibit glucagon based on in vitro studies (39). High-dose glucocorticoids have been shown to be catabolic in rodents showing increased protein breakdown in...
skeletal muscle and suppressed protein synthesis (43,44). In humans, however, it has been demonstrated that a short-term moderate dose of prednisone has no effect on whole-body or leg muscle protein metabolism or muscle function (45). Although epinephrine and norepinephrine are usually associated with catabolic processes, such as stimulation of lipolysis and glycogenolysis through a $\beta$-adrenergic–mediated increase in intracellular cAMP, catecholamines may have an anabolic effect on skeletal muscle protein metabolism (46).

The regulation of BCAAs by other hormones is not fully defined. Growth hormones may play a role in protein dynamics directly and perhaps via Insulin-growth factor-1. Net protein balance is increased with growth hormone (47,48) and Insulin-growth factor-1 (47,49–52). Leucine oxidation was reduced significantly when growth hormone was given, but there was no change in carbon dioxide production or whole-body leucine flux. Nonoxidative disposal of leucine was marginally higher in growth hormone–treated patients, but this effect is largely due to nonmuscle tissues (47). IGF-1 has been shown to act somewhat like insulin, with its anabolic effect largely due to inhibition of protein breakdown with a similar effect on BCAA levels, as in the case of insulin administration (53,54). Testosterone has been shown to increase skeletal muscle protein synthesis (55). However, muscle protein degradation was not measured, and testosterone has no known effect on BCAAs.

**BCAAs and aging.** In aging, there is sarcopenia and decreased protein synthesis. In the muscle, myosin heavy-chain synthesis rates are decreased in the elderly, whereas sarcoplasmic protein synthesis is either maintained or increased (56). Essential AA and total AA administration have been shown to enhance muscle protein synthesis in the elderly (57), but their specific effect on BCAA levels is not as well studied. With age, potency of AA to elicit hormone secretion may decrease. Leucine and isoleucine have been shown to stimulate insulin release, but this stimulatory effect on insulin secretion is not as strong with age (38,58). Furthermore, in our studies, we have shown a progressive decline in human mitochondrial function with age (56) via a decline of mitochondrial DNA copy.

**FIGURE 3** Insulin’s effect on protein synthesis and degradation The study conditions are saline infusion (NS), insulin alone (Ins), AA infusion to maintain plasma AAs during insulin infusion (LoAA/Ins), infusion at high physiological AA infusion with insulin (HiAA/Ins), and somatostatin with replacement of insulin, glucagon, and growth hormone with high physiological AAs (SRIH/AA) or saline (SRIH/NS). Changes in protein synthesis and protein breakdown from baseline values are shown. Both muscle and splanchnic regions are given. The calculation of muscle assumes that leg represents 25% of total muscle mass in the body. *Difference from baseline, $P < 0.05–0.001$; a, different from NS ($P < 0.05–0.001$); b, different from Ins ($P < 0.05–0.001$); c, different from LoAA/Ins ($P < 0.001$); d, different from SRIH/NS. Reproduced from Nygren and Nair (27).

**FIGURE 4** Glucagon effect on BCAA levels. Stable isotope of an essential AA (l-[1–13C]leucine) was used as a tracer of in vivo protein metabolism. A combined deficiency of insulin and glucagon was induced by intravenous infusion of somatostatin. Hyperglucagonemia and hypoinsulinemia were induced by infusions of somatostatin and glucagon. There was a statistically significant increase in isoleucine and valine, decrease in lysine and alanin, and no significant change with leucine. SS, somatostatin; SS+G, somatostatin and glucagon. *$P < 0.05$. Adapted from Nair et al. (41).

**FIGURE 5** Glucagon effect on leucine kinetics in nondiabetic people. Stable isotope of an essential AA (l-[1–13C]leucine) was used as a tracer of in vivo protein metabolism. A combined deficiency of insulin and glucagon was induced by intravenous infusion of somatostatin. Hyperglucagonemia and hypoinsulinemia were induced by infusions of somatostatin and glucagon. The increase in leucine flux during the infusion of somatostatin and glucagon was higher than the increase during infusion of somatostatin alone ($P < 0.01$, paired $t$ test). Somatostatin alone did not change leucine oxidation, whereas the somatostatin plus glucagon increased leucine oxidation 100% ($P < 0.05$). This suggested that hyperglucagonemia accelerated proteolysis and leucine oxidation in insulin-deficient humans. SS, somatostatin; SS+G, somatostatin and glucagon. Adapted from Nair et al. (41).
numbers and rates of ATP production (59). AAs along with insulin have been shown to enhance muscle mitochondrial biogenesis, although it is unclear whether age impacts the effects of AAs and insulin. Because BCAAs are the key signaling molecules, it is possible that muscle mitochondrial effect is mediated by BCAAs (60). The mitochondrial decay with age may have importance on BCAA metabolism because branched-chain \( \alpha \)-ketoacid dehydrogenase, the rate-limiting step in catabolism, is exclusively mitochondrial. With age, there is also decreased muscle mass and, with that, there is potential decreased capacity to oxidize BCAAs. For example, leucine oxidation when corrected for lean tissue is not different in young and older people (61), suggesting that absolute leucine oxidation is lower in older people. The elderly are also more at risk for nutritional deficiencies and, as we described before, that can impact BCAA metabolism. There is continuing controversy over whether older people require higher amounts of BCAAs than younger people (62).

**BCAAs and stress.** During surgery, infection, or burns, there is an increase in resting energy expenditure and body temperature. Stress causes release of counterregulatory hormones, including epinephrine, cortisol, glucagon, etc. This leads to a marked increase in the release of AAs from tissue proteins (except a transient decrease of AA from protein breakdown has been reported following epinephrine infusion [63], especially skeletal muscle). First, the newly released BCAAs are deaminated and the resulting \( \alpha \)-ketoacids are oxidized as source of energy while the amino groups are utilized in synthesis of alanine, glutamate, and glutamine, which are used for gluconeogenesis. Part of the ketoacids is also released in the bloodstream to be taken up by the liver for ketone body synthesis (64). Second, there is an increase in hepatic gluconeogenesis. Third, there is an increase in the synthesis of specific proteins (acute phase response). What remains to be determined is whether providing an extra amount of BCAAs favorably affects the metabolic profile and outcome of patients during stress (13).

In sepsis, one study showed BCAA levels were decreased significantly. These changes were more pronounced in severe sepsis (65). In burn patients, plasma AAs fell primarily due to nonessential AAs. Interestingly, alterations in muscle free AAs generally were similar to plasma AAs (except that for alanine and glycine) (66). Initially, BCAAs remained unchanged for the first few weeks and then rose markedly (67).

**BCAAs in renal and liver insufficiency.** BCAAs do not increase glomerular filtration rate, a measure of kidney function, which is perhaps useful in the setting of kidney disease. Increased protein intake is a factor that causes deterioration of renal function in patients with kidney failure, but providing essential AAs, especially BCAAs, is important to prevent protein malnutrition and wasting of lean tissue. Protein and BCAA metabolism have been studied in rats that underwent nephrectomy. Twenty-eight days after surgery, there was a drop in BCAA levels and a significant rise in urea and creatinine in plasma after constant infusion of labeled leucine. In nephrectomized rats with acidosis, there were significant increases in protein degradation, leucine oxidation, leucine oxidized fraction, and leucine clearance. A significant decrease in valine concentration in muscle was found. This suggests that marked activation of protein degradation occurs in severe chronic renal failure and is probably caused by metabolic changes related to development of acidosis. It has been shown that the kidney plays a key role in the production of tyrosine from phenylalanine in vivo (68); therefore, tyrosine deficiency occurs during end-stage renal disease (69). The effect of kidney failure on BCAA metabolism is not clear (70).

In hepatic insufficiency, BCAAs are useful because they are not metabolized in the liver, but there is nevertheless altered leucine kinetics. Therefore, plasma BCAA levels may be difficult to interpret. In fulminant hepatic failure, BCAA levels are either normal or increased (71). However, in states of extensive portal-systemic collateral circulation, plasma levels of BCAAs are low in association with hyperammonemia (72). Cirrhosis is associated with increased circulating levels of glucagon (73), which may cause increased leucine oxidation. In addition, cirrhotic patients have decreased nonoxidative leucine disposal and are unable to suppress endogenous protein degradation normally in response to AA administration (74). These abnormalities may contribute to the diminished fat stores and body cell mass commonly observed in cirrhosis (75). In cirrhosis, there is a reduction in albumin synthesis (76). It has been shown in rats that BCAAs promote albumin synthesis through the mammalian target of rapamycin-independent signaling pathway (77). In response to the AA infusion, total leucine appearance from protein degradation and leucine incorporation into protein increased significantly in cirrhotic rats (70). Data suggest that the extent of leucine carbon oxidation is dependent on whether fat or carbohydrate is the prevailing fuel substrate. Following combined infusion of tracer with branched-chain-enriched, aromatic-deficient AAs, insulin, and euglycemic clamp in cirrhetics, net protein deposition increased normally despite a blunted response of protein synthesis. In nonalcoholic steatohepatitis, there is reduced apo B100 protein synthesis, although not necessarily albumin synthesis (78–80). It remains to be determined whether administration of BCAAs enhances protein anabolism, especially synthesis of albumin and apo B100 in nonalcoholic steatohepatitis and cirrhosis (81).

**Potential biomarkers of BCAA status**

An ideal biomarker should be a simple test that can be clinically available. Because BCAA levels or their ketoacids are unlikely to be reliable markers of BCAA status, future research has to focus on other reliable biomarkers that represent the fate or impact of BCAAs. Leucine oxidation is a logical choice, but leucine oxidation is affected by a variety of factors, including hormones that increase in many pathological states that may require BCAA administration. Recent advances in proteomics (82) and the emerging field of metabolomics (83) offer the opportunity to identify potential biomarkers that can be measured in biological samples such as urine or plasma. A variety of techniques provide a functional analysis of protein metabolism, including isotope tracer approaches in combination with mass spectroscopy to identify changes in protein synthesis rates.

**Conclusion**

There are many clinical conditions that may benefit from BCAAs. Unfortunately, there are no reliable markers to assess status or quantify their requirements such that the dose and duration of their administration can be monitored. BCAA levels are unreliable because fasting causes increased levels of BCAAs, and poor nutritional status can lead to increased catabolism of BCAAs. BCAAs favor the protein anabolic pathway. BCAAs are not a significant energy source during exercise when compared to carbohydrate or fat. They participate in interorgan nitrogen transfer. They are important nitrogen donors to glutamine and alanine, which are important glucose precursors and fuel for the gut. They have a complex interaction with hormones, with glucagon being a key regulator of leucine oxidation. Leucine and isoleucine can stimulate
insulin release, especially in children in which they may inhibit glucagon. With age, there is some evidence that there is decreased potency of AAs. BCAA metabolism may be affected by renal or liver dysfunction. Although we do have knowledge of BCAA kinetics, the interaction of hormones and the underlying nutritional and clinical state need to be considered when interpreting levels. Consideration should be given to the importance of BCAA levels in specific tissues, such as muscle as opposed to plasma levels. Future search for biomarkers of BCAA status may utilize the emerging large-scale measurement approaches, proteomics and metabolomics, which provide valuable tools to monitor the needs of BCAAs in humans.

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