TECHNICAL PAPER ON CLINICAL APPLICATIONS OF A NON-CALORIC BEVERAGE CONTAINING AMINO ACIDS

PREPARED FOR GOOD IDEA®, INC.

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Overview/Summary

Late-breaking research is coalescing to support the assertion that dietary protein is more nuanced than previously understood. Proteinogenic amino acids have distinct metabolic pathways and exert clinically meaningful effects on glucose homeostasis, ageing and post-operative recovery.

Elevated branched-chain amino acids (BCAAs) in the bloodstream are a backlogged supply of substrate. This is observed in patients with metabolic dysfunction, most commonly diabetes. Elevated BCAAs thus serve as a research biomarker and it is interesting to better understand metabolism including the factors which determine mTOR.

Good Idea® is a combination treatment with several active ingredients – select amino acids, chromium, and a noncaloric, alkalinizing beverage. It is the only BCAA-containing product that by merit of its other ingredients is mTOR neutral. Good Idea® works optimally when used in conjunction with healthful lifestyle and dietary patterns.

Background on amino acid therapies in chronic diseases

New diseases have given rise to new therapies including specific amino acids. Nutritional research has long emphasized protein as a macronutrient, because until recent decades the most prevalent nutrition-related disease was malnutrition. Considering protein as a macronutrient enables researchers to compare all diets around the globe to determine the adequacy of food supplies. However, today's chronic disease epidemic requires a different set of research priorities. Studying the individual amino acids which comprise proteins has enabled the development of novel amino acid therapies for the chronic disease epidemic [1].

In the past several decades different amino acids and related organic acids have been researched for their metabolic effects. The amino acid combinations found in animal-sourced dietary protein build muscle more than plant-based protein [2]. In 2003 Dr. Elena Volpi demonstrated that the 9 essential amino acids are the amino acids responsible for stimulating protein metabolism in healthy elderly [3 4]. At that same time endocrinologist Dr. Diana Schwarzbein published her clinical observations on amino acid supplementation in her patients with obesity and diabetes [5]. The two key opinion leaders led a scientific forum at the Annual Conference of the Institute for Functional Medicine more than a dozen years ago. Today the work of both physician scientists work has been corroborated and greatly expanded [6].

Notably, BCAAs from diet and supplementation have been shown to prevent muscle atrophy in aging and immobility (disuse atrophy) [7 8]. Science can now explain how exercise and amino acids interact to preserve muscle, both at the cellular level and clinically [9 10]. When two additional essential amino acids, lysine and threonine, are combined with BCAAs such as in whey protein, the metabolic effects may be more favorable [10 11]. The metabolic complexity has prompted a recognized need for long-term, realistic strategies [12]. Good Idea® is a realistic strategy which incorporates the three BCAAs, lysine and threonine.

The biochemical basis of BCAA therapies

What is sometimes under-recognized is that the clinical observations are based on metabolic pathways. Those metabolic pathways are, in turn, largely determined by the molecular structure of the amino acid side chains. **Figure 1** illustrates the molecular structures of the 21 proteinogenic amino acids, which are those that form protein bonds. The biochemical basis for BCAAs' touted clinical roles is presented here.

1. The BCAAs are three - isoleucine, leucine and valine and they are all essential, meaning that the human metabolism cannot synthesize them from scratch. Thus, they must be sourced from the diet. It is also possible that they are formed by microbial sources in the gut.

2. BCAAs derive their name from their methyl branch. The BCAAs are the only 3 of the proteinogenic amino acids with an aliphatic branch. On the molecular structures depicted in **Figure 1** the branch resembles a Mercedes Benz symbol.

3. The methyl group necessitates that these 3 amino acids are metabolized by a specialized and rate-limiting enzyme called branch chain amino acid (BCAA) transaminase. The metabolic fate of the BCAAs at any given time is influenced by the rate of activity of the BCAA-transaminase.

4. BCAAs side chains are aliphatic – carbon chains which are not organic. Aliphatic compounds are hydrophobic, the least miscible in aqueous solutions. Conversely they are lipophilic, miscible in fatty structures. Thus, BCAAs aggregate in lipid spaces such as neurologic signaling pathways.

Figure 1 shows the biochemical characteristics which BCAAs do not possess. These can also be informative. BCAAs are not delivery vehicles for specific nutrient cargo such as sulfur or organic ring

structures. Amino acids with nutrient cargo tend to be quickly metabolized once their cargo is off-loaded - not BCAAs. Some amino acid side chains are positively or negatively charged at physiologic pH and some are polar – not BCAAs. BCAAs would be anticipated to respond differently than other amino acids to changes in the metabolic milieu - pH, temperature, and hormonal shifts.

In summary the BCAAs are three essential, proteinogenic amino acids containing an aliphatic branched side-chain that is metabolized by a common enzyme.
BCAAs are slow to undergo transamination, and lysine and threonine seldom undergo transamination. Since transamination is the common biochemical process by which most amino acids are degraded, lysine and threonine are biochemically thought to work in tandem with BCAAs.

Blood levels of BCAAs are newly viewed as a biomarker

In 2017 researchers demonstrated that elevated plasma levels of BCAAs were associated with elevated risk of diabetes and indirectly to cardiovascular disease risk [13-15]. In other words, people with diabetes and hypertension average higher blood levels of BCAAs. The scientific community jumped on this topic quickly, for good reasons. BCAAs may be a new blood biomarker, one that could potentially be used to guide the treatment of common chronic diseases. Since biomarkers can be targets for drug therapies, they are often intensively researched by scientists in drug discovery.

High blood levels of BCAAs are the effect of metabolic diseases, not the cause

Elevated blood BCAA levels are interesting biomarkers to be sure, but biomarkers do not imply causality. Instead, elevated blood BCAAs are thought to be the result of metabolic diseases and not the cause. Below 4 different lines of reasoning are presented.

1. **Biologic plausibility.** BCAAs are slow to be metabolized on merits of their biochemistry reviewed above. Their branches, hydrophobic properties, rate-limiting enzyme, and "essential" status gave rise to evolutionary advantage to holding on to BCAAs. Further to this point, protein synthesis involves more than the presence of amino acid substrate. Synthesis and repair of protein structures is deferred during unfavorable metabolic conditions such as pH, temperature, salinity, viscosity and hormonal imbalances. Consequently, basic biochemistry points to proteinogenic amino acids being back-logged, and BCAAs conserved preferentially. Since diabetes is a state of dysmetabolism, blood BCAA levels would then be anticipated to be high.

   Some scientists have reasoned that BCAAs may be causal because they raise mTOR as noted in 2000 [16]. Fasting, in contrast, induces autophagy and lowers mTOR [17 18]. Amino acids in the circulation communicate a non-fasting state and, in this way, raise mTOR. **Figure 2** diagrams currently known lifestyle factors which raise and lower mTOR. The net impact on mTOR would be the clinically meaningful value, not the effect of BCAAs on mTOR alone.

2. **Clinical observation.** Clinicians who are familiar with how diet can influence blood tests would find ready examples of metabolic backlogs. A similar scientific debate ensued in the 1990s over the cause of elevated triglycerides. Build-up of triglycerides is not from eating natural fats as

originally claimed, but rather from diets high in refined carbohydrates. The refined carbohydrates shift metabolic priorities, so that the processing of blood fats is slowed [19].

Another dietary cause of triglyceride-mediated heart disease and metabolic syndrome globally is synthetic *trans* fats [20]. The *trans* fats have a different configuration which confuses metabolic processes. Interestingly there are naturally occurring *trans* fats in dairy products, synthesized by the gut microbiome in the lactating female. One of these, conjugated linoleic acid, promotes weight loss and the accretion of muscle [21]. That may be because this naturally occurring *trans* fat lingers in the blood stream where it has evolved over millennia to signal satiety. Synthetic *trans* fats would not be expected to signal satiety because they are an "unknown" entity without evolutionary traction, and their concentration in the human diet is roughly hundred-fold greater than naturally occurring trans fats.

The key point is that nutrients with atypical molecular configurations such as branches and *trans* conformation linger in the bloodstream. There they can decrease hunger and promote muscle synthesis which can be clinically observed.

3. **Oral challenge.** The research to date has not demonstrated that dietary intake is the cause of high BCAA plasma levels. In fact an extensive review identified many metabolic pathways that lead to high BCAA levels in health and disease [22].

4. **Epidemiology.** Epidemiologic studies do not support causality outside of diabetes where there is an obvious build-up of substrate. For example, The Women's Health Study has provided researchers with a robust longitudinal database. While the database showed an association between plasma BCAAs and the dysmetabolic state of diabetes, it did not show an association with cardiovascular disease risk once diabetes level was controlled [14]. That is another way of stating that only diabetes, not BCAAs, cause heart disease.

Caveat mTOR: Why Good Idea® is a metabolically great idea

BCAAs, lysine and threonine are the amino acids in Good Idea® based on their studied therapeutic roles: improve satiety [23], maintain muscle [10], reduce postprandial glycaemia [24] and manage subjective, short-term food cravings [10 25]. BCAAs are likely to signal these metabolic effects by circulating in the bloodstream before being metabolised. In patients with metabolic disease such as diabetes, blood levels of BCAAs become high since the metabolic problems may prevent protein synthesis. Thus they can now serve as a biomarker which will help scientists study how diseases such as diabetes change metabolic pathways and how to correct them.

Not all BCAA supplements are alike. Research points to Good Idea® being a superior amino acid source in the following ways:

1. Good Idea®'s novel approach is to frontload BCAAs. Giving BCAAs before a meal avoids competition for the enzyme. The premeal BCAAs are metabolized before the substrate from the meal.

2. Good Idea® provides BCAAs in a non-caloric setting [26]. BCAAs raise mTOR but caloric restriction lowers mTOR. In sum mTOR would not be higher or lower. There would be net neutrality.

3. Derailed by cravings and muscle loss, diets often fail despite best efforts. Good idea® is a combination therapy. It contains multiple methods of appetite control including chromium a neuroactive mineral messenger of satiety [27]. When given before meals it preloads protein which gives the brain a jumpstart on satiety signaling. Furthermore, it satisfies thirst without calories. Thirst is regulated more tightly than hunger [28], highlighting the importance that thirst be satisfied by a non-caloric beverage.

4. Enzymes such as BCAA transaminase function optimally at a select pH. In diabetes and most forms of metabolic dysfunction blood pH tends to be on the acidic side of optimal. In diabetes, uncontrolled pH can be dangerously low. Good Idea® drinks contain citrate which is a substrate for the Kreb's Cycle and provides bicarbonate. So while the physical chemistry or pH of citrate is acidic, biochemically it can be alkalinizing in some body fluids. The citrate in Good Idea® might therefore be considered an active ingredient by promoting acidic pH in the stomach to absorb amino acids, and donating bicarbonate to metabolic pathways.

Clinical applications

The BCAAs are used to treat diverse clinical conditions, all which impose on muscle metabolism. Supplementing BCAAs can safeguard muscle. There are three clinical specialties where a novel BCAA-product may most readily be introduced.

Bariatric medicine

Weight reduction is complex. This complexity has driven the recognition that weight maintenance is most effective with combination therapy [29]. The FDA has been formally requested by U.S. Congress to actively seek industry innovation for obesity therapies. Now first line pharmacotherapy involves medications with multiple mechanisms in one pill. It is required of weight management programs to prescribe lifestyle modification as part of the combination therapy. Amino acids which activate satiety centers of the brain would be a new obesity treatment, potentially combined with other therapies.

Weight reduction is difficult because of food cravings which at times are disabling. Therapies which take aim at food cravings help dieters control portion size and food selection. A novel BCAA therapy which can be strategically timed to reduce food cravings would potentially improve diet adherence.

Dieting can unfavorably redirect metabolic pathways. Importantly, in the setting of diet-induced weight loss amino acids are sometimes degraded for glucose synthesis, the way carbohydrates are catabolized. Protein is then not available for muscle synthesis. The essential amino acids provide the needed protein in the setting of diet-induced weight reduction, and at the same time stimulate muscle protein synthesis even in the setting of diet-induced weight loss.

Dieting leads to loss of both fat mass and lean body mass [10]. Failed weight reduction, when the diet-induced weight loss is regained, a higher proportion is fat mass. Someone who loses weight and then gains it back has more fat mass than at the start. In other words, the scale may read the same but the proportion of the amount of weight which is lean muscle is less. Since muscle is more metabolically active than fat, the metabolic rate is also reduced. BCAAs which preserve muscle during times of decreased food intake such as dieting would be anticipated to make dieting safer.

Whole-body protein building has been shown to be reduced when absorption of amino acids is decreased. This has been shown in the absence of disease or gastrointestinal surgery. When the patient has a medical condition or prior gastrointestinal surgery, absorption of amino acids is more likely to determine lean muscle mass. Some bariatric surgical procedures can affect the amount of dietary protein which is absorbed. Even those surgeries which are not malabsorptive *per se* can reduce protein absorption. Protein is dependent on adequate time and digestive juices in the stomach to break down the fiber matrix so that the protein can be absorbed. Therefore following bariatric surgery BCAA supplementation would seem prudent.

The optimal timing for protein intake is throughout the day. This facilitates a steady supply of amino acids in the circulation during times when muscle synthesis is marginal, such as dieting, immobility, surgery and atrophy of aging. Some dieting programs do not endorse eating throughout the day. Therefore a non-caloric beverage with essential amino acids can be consumed between meals to do both – maintain optimal amino acids in the circulation and adhere to scheduled meals.

Combination products for appetite control are not limited to pharmaceutical therapies and amino acids. The mineral chromium has been demonstrated to superiorly preserve lean muscle in the setting of diet-induced weight reduction [30]. A novel combination of essential amino acids and chromium picolinate would therefore be considered a combination therapy intended to preserve lean mass in the setting of diet-induced weight reduction.

<u>Integrative Medicine</u>

Diabetes is managed in diabetes clinics. Diabetes is treated in integrative medicine practices. The terms “manage” and “treat” differ in expectation [1]. Of particular note ketogenic amino acids which include the BCAAs may favorably influence several of the chronic conditions associated with diabetes including fatty liver disease [31]. A novel BCAA product can be integrated into the treatment of diabetes, with the goal of resolution of symptoms.

Geriatrics treats patients with advanced chronologic age. Integrative longevity medicine aims to lower biologic age. For example, integrative physicians recognize that protein requirements increase in the elderly, in contrast to most nutrients which decrease in old age since metabolism slows. The increased protein needs in the elderly is attributed largely to the inability to digest and absorb protein due to a decline in stomach acid with aging [32]. BCAA supplementation is integral to the integrative treatment of sarcopenia of aging[10] . Some integrative longevity medicine specialists take a dietary history noting not only the protein intake but the intake of BCAAs as well [10].

Physical Medicine and Rehabilitation

BCAAs especially leucine supplementation is recommended perioperatively in physical medicine programs [33]. Surgery roughly doubles protein requirements. Immobility is common before and after orthopedic surgery. Consequently, muscles atrophy from disuse is a metabolic side effect of surgery which can be minimized with BCAAs [33]. Bone and surgical wound healing are influenced by adequacy of protein [34].

Other fields of medicine

Key opinion leaders across medical specialties recommend their patients BCAAs. These forward-thinking clinicians include:

- Pharmacists aware of the adverse effects of medications on muscle tissue, recommend adequate protein with special attention to BCAAs [35] .
- Some orthopedic surgeons treat patients for even mild protein malnutrition because it is a treatable caused of delayed fracture healing and surgical nonunion of bones [34].
- Dentists can infer the condition of system soft tissue based on the condition of their patients' teeth, gums and oropharyngeal space. This inside look has led some of them to be proponents of dietary BCAAs [36].
- Nephrologists instruct patients with certain kidney diseases to minimize protein intake because it can cause the kidney to fail more quickly. Measured intake of BCAAs can keep protein intake low and yet meet metabolic requirements for preserving muscle mass [37].
- There are heritable factors in metabolism, particularly how diet and genes work together to regulate mTOR. Some clinicians specialize in helping patients use their genetic tests to guide nutrient supplements including BCAAs [38].

Conclusion:

Until the scientific community took interest in plasma BCAA levels many clinicians did not look beyond protein as a macronutrient. There was little interest in the now numerous clinical uses for specific amino acids. Potentially the surge in interest in amino acids can prompt clinicians and their patients to notice Good Idea®.

Not only does scientific research position Good Idea® as a BCAA-product, it is a combination therapy using BCAAs, chromium, non-caloric hydration and a net-neutral effect on mTOR.

Marketing direct to consumer can be combined with clinical recommendations by health care providers. Three fields of clinical medicine have a perceived need for therapies which achieve the clinical results demonstrated by Good Idea®.

Figure 1. Molecular structures of amino acids, comparing and contrasting BCAAs

Accessed on the Difference Between website on Feb 22, 2019. Posted by Madhu on July 3, 2018. Weblink: **https://www.differencebetween.com/difference-between-bcaa-and-amino-acids/**

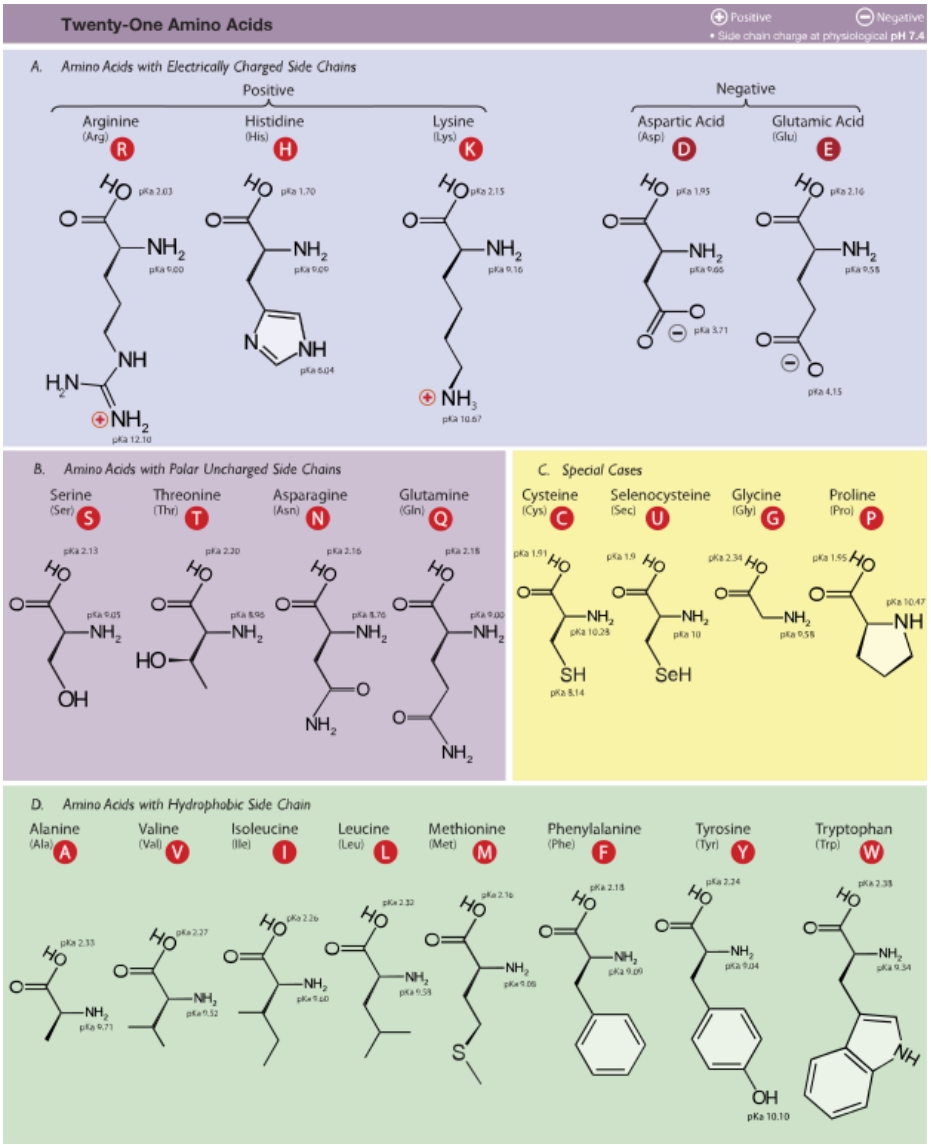

Figure 2. Metabolic pathways influencing mTOR.

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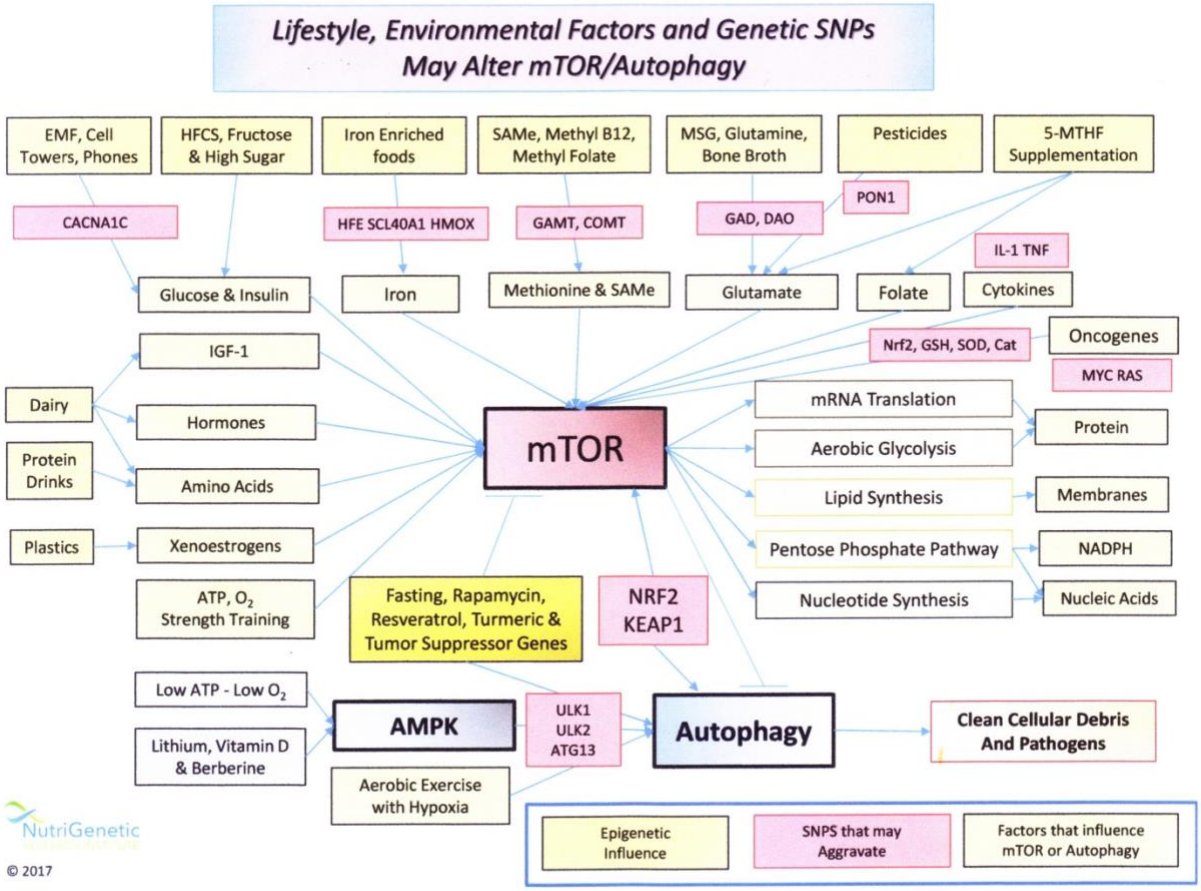

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