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Branched Chain Amino Acids and Risk of Type 2 Diabetes Mellitus: A Literature Review

Alina Yemelyanov

ABSTRACT

Branched Chain Amino Acids and Risk of Type 2 Diabetes Mellitus: A Literature Review

By

Alina A. Yemelyanov

November 20th, 2020

INTRODUCTION Type 2 diabetes mellitus (T2DM) is recognized as a major public health problem in the modern world, with its prevalence increasing each year. Consistently poor lifestyle habits — namely, nutritional excess coupled with sedentary behavior — are the leading causes of obesity, which in turn leverages the gradual desensitization of cells to insulin, followed by the onset of insulin resistance (IR) and the subsequent development of T2DM.
Countless studies and ongoing research have confirmed that nutrition plays a definitive role in contributing to the development and onset of T2DM. However, in recent years, there has been increasing controversy surrounding the role that branched-chain amino acids (BCAAs) may play in influencing IR and the development of T2DM.

AIM To review existing literature regarding both the purportedly harmful and beneficial roles and impacts of BCAAs on metabolic health, in order to better understand the contradictory nature of BCAAs and their effects on IR and T2DM.

METHODS Relevant research, review articles and epidemiological studies spanning the timeframe from 2004 to 2020 were collected, analyzed and summarized with the goal of underscoring and delineating the conflicting roles of BCAAs.

RESULTS Evidence of beneficial effects of BCAAs includes enhanced muscle protein synthesis, more efficient glucose homeostasis, increased satiety, better body composition and improved body weight regulation. Evidence of harmful effects of BCAAs includes elevated fasting concentrations of circulating BCAAs correlating with an increased risk of IR and T2DM in human and rodent models.

DISCUSSION In spite of the various studies that have been undertaken to shed further light on BCAAs, it still remains unclear whether they are simply *markers* of metabolic disturbances that ultimately lead to the development of T2DM, or if they are, at least in part, the actual *cause* of metabolic disturbances leading to T2DM. The general consensus amongst the scientific community is that more research is needed on this topic.

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BRANCHED CHAIN AMINO ACIDS AND RISK OF TYPE 2 DIABETES MELLITUS: A LITERATURE REVIEW

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Author's Statement Page

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Alina Yemelyanov

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I. INTRODUCTION

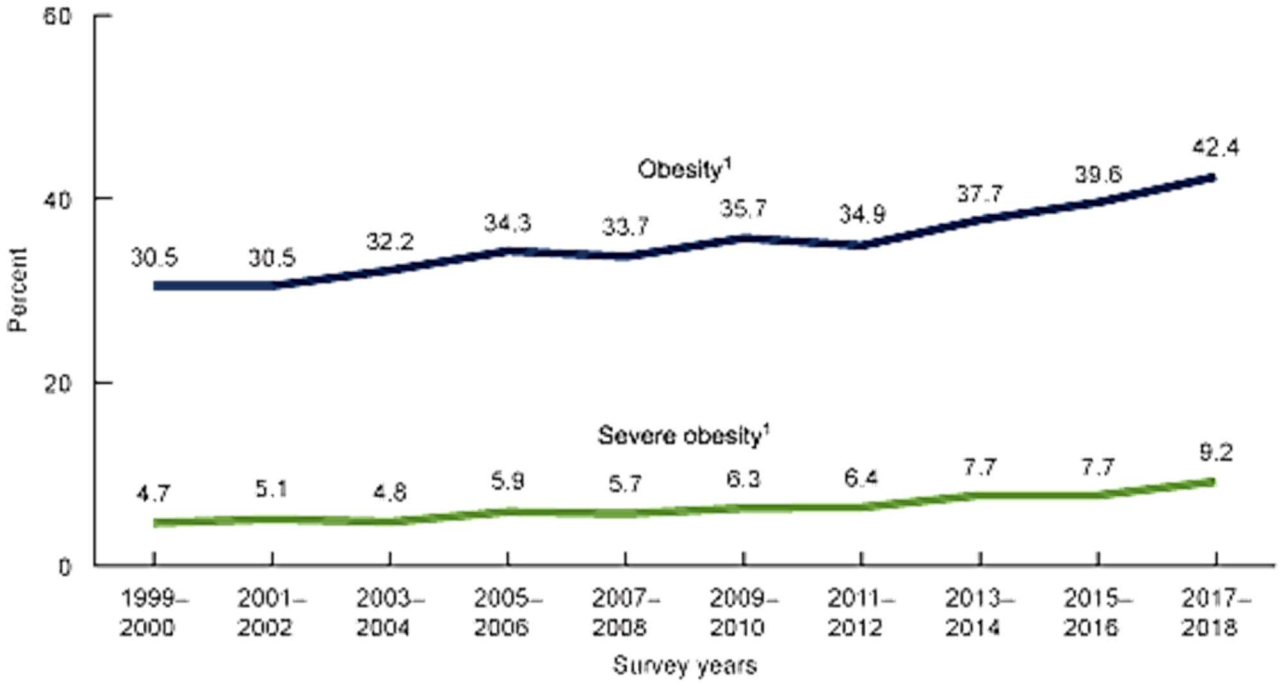
1.1. Type 2 Diabetes Mellitus as a Public Health Problem

Within the context of public health, type 2 diabetes mellitus (T2DM) has come to the forefront as a prevalent chronic disease in our modern world, having led to significantly escalating morbidity and mortality, while contributing to a large spike in associated healthcare expenditures [5]. The prevalence of T2DM worldwide has been skyrocketing in recent years, to the extent that it is now being recognized as one of the primary threats to human health and wellness [14]. In the United States, this chronic disease has already taken a considerable toll on public health, burdening approximately 9% of the entire population [2], while global estimates indicate that upwards of 380 million adults worldwide suffer from T2DM; however, this number is projected to continue rapidly increasing in prevalence over the course of the next 20 years [5]. In American adults, T2DM accounts for approximately 90-95% of all diagnosed cases of diabetes, but the majority of all cases can be prevented or delayed simply by leading a healthier lifestyle [16].

Over the long term, poor lifestyle factors play a determining role in influencing the gradual development of T2DM: ongoing nutritional excess coupled with sedentary behavior tend to lead to obesity, and this metabolic disorder becomes a major precursor to developing T2DM, while acting to increase the secretion of insulin [2]. In fact, being overweight or obese is considered to be the primary risk factor for T2DM, while leading a sedentary lifestyle makes healthy weight maintenance less manageable, since cells gradually become less sensitive to the effects of insulin, and glucose is not expended as readily for energy [9]. Moreover, obesity in and of itself has become an escalating global health problem, posing a major risk factor for the onset and development of metabolic syndrome, T2DM and other debilitating chronic conditions [7].

Along with T2DM, the issue of obesity has become of far greater concern to public health in recent years. Over the last four decades, its prevalence has radically increased. It is estimated that in the United States alone, more than two in three adults are now considered to be overweight or obese [15]. According to the latest data from the CDC, in 2017-2018, the age-adjusted prevalence of obesity among U.S. adults was 42.4%, while the age-adjusted prevalence of severe obesity among U.S. adults was 9.2% [18].

FIG. 1. Trends in age-adjusted obesity and severe obesity prevalence among adults aged 20 and over: United States, 1999–2000 through 2017–2018

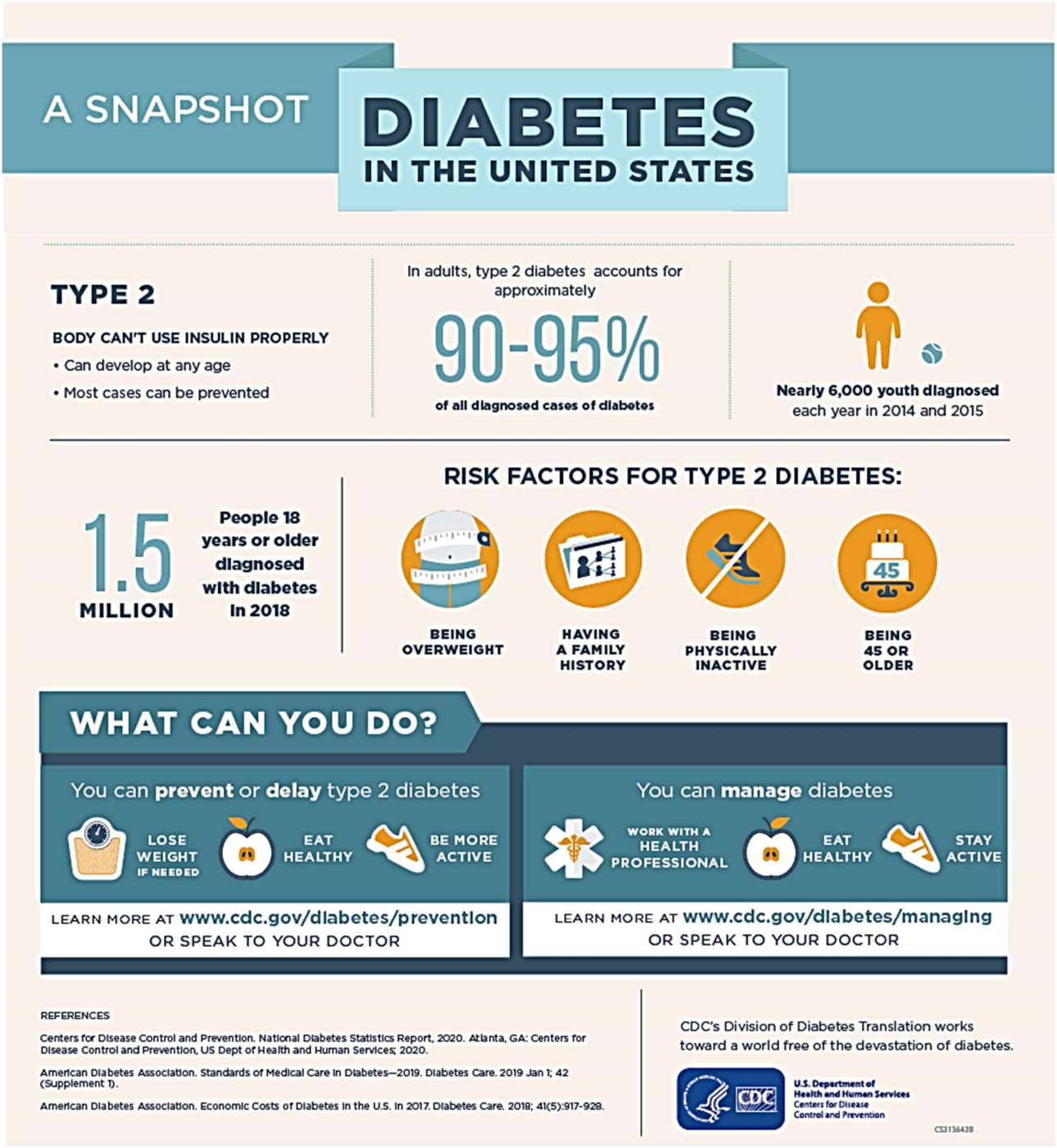


Hales, C., Carroll, M., Fryar, C., & Ogden, C. (2020, February 27).

However, apart from the primary conditions of overweight and obesity, several other factors exist that markedly increase the risk for onset of T2DM, and these include family history, race, ethnicity, age, polycystic ovarian syndrome (PCOS) in women, physical inactivity, and excessive visceral fat distribution [9, 16]. Paradoxically, many obese individuals who carry a

greater proportion of their adipose tissue subcutaneously rather than viscerally do appear to be protected to a greater extent from IR and adverse metabolic responses [2].

FIG. 2. A Snapshot of T2DM in the US



Centers for Disease Control and Prevention. (2020, February 18).

1.2. Etiology of Type 2 Diabetes Mellitus

T2DM is a condition characterized by abnormalities in carbohydrate, protein, and lipid metabolism, with its most characteristic features consisting of hyperglycemia, or elevated blood sugar levels, and dyslipidemia, which indicates abnormally high levels of lipids circulating in the blood [14]. The biological pathway spurring the onset of T2DM involves insulin resistance (IR) at its core. Insulin itself is required to consistently maintain glucose homeostasis [6]. The concept of "insulin resistance" essentially refers to a marked decline in a target cell's metabolic response to insulin secreted by the pancreas; at the level of the entire organism, this translates to the impaired ability of naturally-circulating or injected insulin to effectively lower blood glucose levels [2]. IR has been recognized to play a major role in obesity-related metabolic disturbances, since it is a "hallmark" of both obesity and sedentary behavior, and therefore is a key precursor to developing T2DM [7, 2]. "Peripheral resistance" to insulin action is thought to act as a primary mechanism in causing metabolic syndrome and, eventually, T2DM [1]. Additionally, insufficient and dysregulated secretion of insulin by the pancreas is also believed to play a contributing role in the occurrence of T2DM, along with the characteristic tissue insensitivity to insulin action (IR) [5].

The significance of insulin sensitivity in regards to maintaining metabolic health has been recognized for quite some time; however, until recent years, the specific mechanisms that may induce IR largely remained unclear [6]. Today, this is no longer the case, since current research has finally begun to shed some light on a variety of different mechanisms and potential causal factors. The aforementioned lifestyle factors also play an important role and have a substantial impact on the incidence of IR. "Strong environmental influences" triggering IR include inadequate amounts of regular physical activity, as well as increased consumption of calorie-

dense processed foods and beverages [5]. Additionally, several biochemical mechanisms are known to be responsible for propagating IR, including carbohydrate metabolism, protein metabolism, and fat metabolism [7]. Other factors implicated in IR include issues such as systemic inflammation, physiological stressors, and oxidative stress, although IR appears to have a significant heritable component, as well; moreover, large-scale human genetic studies conducted in recent years have helped identify a more solid link between heredity and IR, while also revealing a key role that reduced mitochondrial function may play in the onset of IR [5].

At present, obesity, metabolic syndrome and T2DM are widespread chronic disorders affecting much of Western society, and the variety of factors involved in the development of metabolic disease are complex [1, 2]. However, the current T2DM “pandemic” is largely thought to be driven by the metabolic decline of those with prediabetes (preDM) into overt T2DM, since the overwhelming majority of patients with preDM already exhibit some form of IR [5]. T2DM itself is considered to be a taxing public health concern and a pervasive chronic disease that presents an extensive burden to the healthcare system. This disease negatively impacts the body on a broad scale, affecting multiple major organ systems, including the nerves, eyes, heart, blood vessels, and kidneys. Long-term complications from T2DM tend to develop gradually, but with time, they can become increasingly debilitating [9]. A variety of serious and potentially life-threatening co-morbidities are associated with T2DM, including the likes of sleep apnea, neuropathy, retinopathy, kidney failure, hearing impairment, slow wound healing, Alzheimer's disease, and vascular morbidities, with devastating complications that lead to ischemic heart disease and nearly 75,000 amputations each year in the US alone [1, 2, 9].

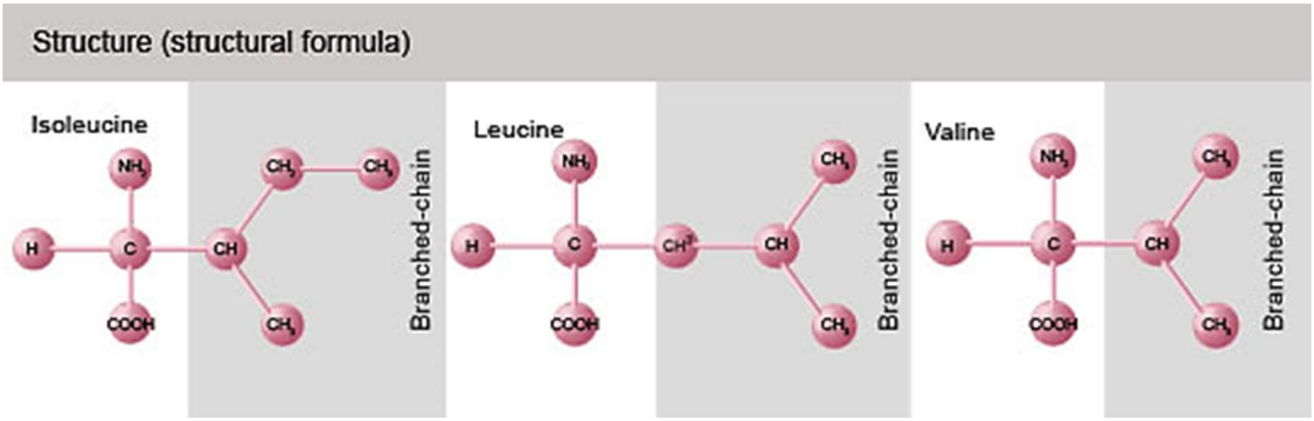
1.3. Branched Chain Amino Acids as a Nutritional Factor

Branched chain amino acids (BCAAs), which consist of leucine, isoleucine, and valine, are essential amino acids that are relatively abundant in dietary proteins, constituting up to 15%-20% of total protein intake; thus, their concentration in blood serum increases after consumption of a protein-rich meal [6, 7, 12]. The typical Western diet is able to provide an ample amount of BCAAs, which means a deficiency is an "exceptionally rare" occurrence. In fact, metabolic and physiological disorders associated with BCAAs usually stem from genetic disruptions, or they originate as secondary disorders to other primary health problems, but not due to deficiency itself [17]. Out of the three amino acids, leucine is the most abundant BCAA found in many dietary proteins, accounting for over 20% of all protein derived from the average human diet [14]. BCAAs are considered to be "essential" amino acids because the body is incapable of synthesizing them from other endogenous compounds at a rate that is essential for healthy growth and functioning, which is why it is necessary to obtain them from a balanced diet [10, 14]. They are referred to as "branched" because this is a descriptive term derived specifically from the structure of their side chains [17].

BCAAs are critical nutrient signals that either directly or indirectly impact the metabolism, supposedly by influencing several catabolic and synthetic "cellular signaling cascades" that help produce altered phenotypes in mammals [6, 3]. Amino acids such as BCAAs are essential for protein synthesis. Therefore, along with the hormone insulin, BCAAs perform the role of anabolic signals, which can alter the growth of energy-consuming tissues, including skeletal muscle and adipose tissue [6], as well as reduce protein breakdown, although the precise mechanisms for this function remain unknown [4].

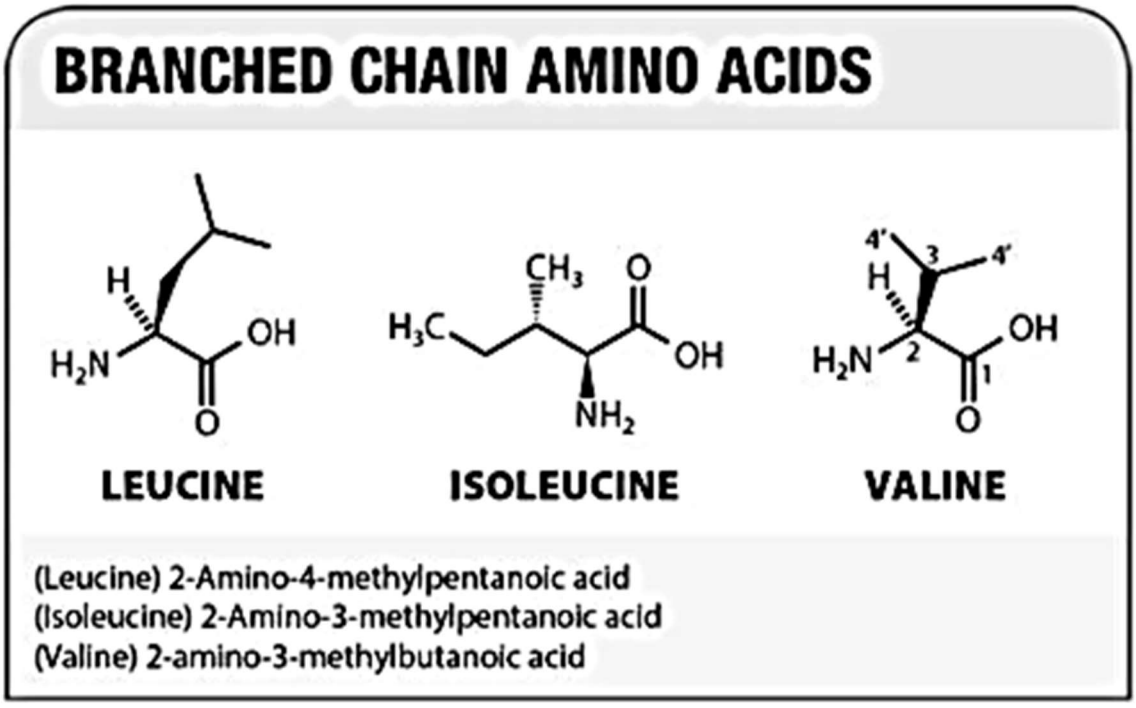
The effects of these amino acids have been studied on a number of disorders, most notably trauma, cancer, sepsis, kidney failure, liver cirrhosis, and burn injury. Supplementation with BCAAs has been alleged to fuel anabolic pathways, consequently helping to mitigate exercise-induced fatigue, promote better wound healing, stimulate insulin production, alleviate cachexia – also known as muscle wasting syndrome – and prevent or treat signs of hepatic encephalopathy caused by severe liver damage [11]. Research has even been undertaken to evaluate the effects of BCAA supplementation on immune response and exercise-induced inflammation, especially as it pertains to strenuous endurance events, such as triathlons and ultramarathons [20]. Although BCAAs are believed to have beneficial health and metabolic properties, there is still no definitive scientific consensus regarding their therapeutic effectiveness, as well as their safe and effective use as nutritional supplements [11]. Despite this, BCAAs have generated substantial research interest in the scientific community due to their emerging roles as potential biomarkers of metabolic disease [14].

FIG. 3.



Andrews, R. (2019, December 30).

FIG. 4.



Petre, A. (2016, November 25).

II. REVIEW OF THE LITERATURE

2.1. The Advantages of BCAAs

Multiple studies have demonstrated various positive effects offered by BCAAs on both animal and human models. Additionally, limited studies have helped illustrate the essential roles that BCAAs play within the physiological regulation of many processes, apart from basic nutrition, and this especially appears to hold true for their role in impacting disease progression [13]. The results from several interventional studies have also proposed that increasing consumption of BCAAs in the diet should leverage an overall positive effect on the parameters associated both with obesity and T2DM, such as satiety, body composition, and blood sugar levels [4].

Because BCAAs – and leucine especially – are such effective protein building blocks, they have garnered substantial interest from the fitness community in recent years, specifically due to their positive effects on enhanced muscle protein synthesis [3]. Not only do BCAAs serve as "substrates" for protein synthesis, they actually stimulate protein synthesis while simultaneously inhibiting proteolysis, or the breakdown of muscle protein [11]. While exhibiting a dominant role in regulating and stimulating protein synthesis, leucine has been identified as a particularly important nutrient signal [3, 4]. It has also been recognized as an active stimulator of both cellular metabolism and mitochondrial biogenesis in "metabolically consequential" cell and tissue types, such as adipose tissue and skeletal muscle [3, 4]. In other words, apart from their anabolic effects, BCAAs may also help proliferate mitochondrial content in both skeletal muscle and fat cells, thus possibly enhancing oxidative capacity and making cells more metabolically efficient [3]. A few studies have also indicated that supplementing with BCAAS before and/or after working out can help reduce muscle soreness that typically follows exercise. Although the specific mechanism responsible for BCAAs' protective effects against exercise-induced soreness and muscle damage is still unclear, it is suspected that leucine in particular may stimulate protein synthesis, while BCAAs may be involved in helping suppress exercise-induced protein breakdown [19].

Furthermore, a positive association has been demonstrated between using BCAA supplementation or consuming a BCAA-rich diet and subsequent metabolic health; essentially, this means that elevating BCAA levels in the body appears to lead to positive health effects, improving such metabolic parameters as glucose homeostasis, satiety, muscle protein synthesis, body composition and body weight regulation [6, 7]. This has been demonstrated in both human and animal studies [7]. The results from Zhao et al.'s systematic review managed to confirm that

a BCAA-rich diet might confer a “weakly positive” impact on peripheral BCAA levels, which can most frequently be explained by the reduced glycemic load inherent in high-protein diets [7]. Insufficient levels of BCAAs in the diet are nonetheless associated with impaired growth and protein wasting. In fact, studies on human subjects have shown that decreased BCAA levels may adversely affect brain function by negatively impacting the synthesis of neurotransmitters. Therefore, BCAA supplementation does appear to be a sensible option in disorders that are characterized by dwindling BCAA levels, which occur during such illnesses as liver cirrhosis, chronic renal insufficiency, and urea cycle disorders [11].

Both direct and indirect mechanisms for some of BCAAs’ positive effects have been suggested; for instance, leucine appears to directly affect the hypothalamic and brainstem processes that are involved in feelings of satiety and reduced hunger. In fat deposits and in the gastrointestinal tract, BCAAs appear to regulate the release of both appetite-stimulating and appetite-suppressing hormones, such as ghrelin and leptin, respectively, and this can potentially impact food intake and blood sugar levels [4]. Additionally, BCAAs in general have also been hypothesized to help enhance overall cell metabolism and improve cellular energetics, after they were shown to activate several regulatory targets involved with increased mitochondrial metabolism [3].

2.2. The Disadvantages of BCAAs

Despite the variety of positive findings purporting the benefits of BCAAs on metabolic health, numerous studies have indicated that these amino acids appear to have a notable downside: along with blood sugar, insulin and certain inflammatory markers, elevated fasting concentrations of circulating BCAAs correlate with an increased risk of IR and T2DM in both humans and in some rodent models [4]. Although the exact underlying mechanisms of the

relationship between BCAAs and T2DM progression, severity and prediction have yet to be fully identified, an imbalance of amino acids – in addition to hyperglycemia and dyslipidemia – may play a pathogenic role, since this imbalance is also a characteristic trait of the diabetic state [14].

In fact, it has been established that in insulin resistant states of obesity, plasma concentrations of amino acids, and BCAAs in particular, tend to be elevated. Previous studies employing metabolomics approaches and extensive metabolic profiling have consistently reported that obese, insulin resistant or T2DM rats and humans both exhibited a disturbance of normal amino acid metabolism, as well as an increased level of circulating BCAA-related metabolites [4, 6, 7]. These findings overlap with studies showing that in experimental settings, an influx of amino acids induces IR, similar to what is witnessed with lipid administration. Recently, growing evidence has demonstrated an interaction between BCAAs and excess fat, as well as between BCAAs and excess protein consumption. More specifically, adding BCAAs into a high-fat diet contributes to the onset of impaired glucose homeostasis and IR, both of which can occur independently of body weight [14]. Additionally, several contemporary studies have come to the conclusion that consuming high levels of protein, which is entirely composed of amino acids, is correlated with IR, T2DM, and increased mortality in both mice and humans, while low protein (LP) diets appear to be associated with better metabolic health and increased survival [15].

BCAAs are considered to be particularly sensitive to insulin action, as their metabolism has been observed to be “profoundly altered” during insulin resistant states [1]. IR is often associated with mitochondrial dysfunction and stress signaling [14]. These two processes are energy sources and believed to be triggered by an abnormal BCAA metabolism in obesity, which results in an accumulation of toxic BCAA metabolites, especially in insulin resistant subjects [6,

14]. Indeed, while it has been established that BCAAs are undoubtedly necessary for protein synthesis, some of the intermediates formed during their catabolism can actually be toxic at high concentrations. Therefore, the efficient disposal of excess BCAAs from the body is in fact vital for maintaining homeostasis and overall metabolic health [19]. Circulating levels of BCAAs tend to be elevated in individuals with obesity, impaired fasting glucose levels and T2DM [4, 14], although morbidly obese individuals who have elevated levels of BCAAs usually see these levels normalize after undergoing gastric bypass surgery [14].

Due to their prevalence in the aforementioned metabolic disturbances, BCAAs are believed to have the potential to predict development of T2DM and obesity, while being associated with worse metabolic health overall, as well as the likelihood for future onset of IR or T2DM [4, 13, 14]. Levels of BCAAs also correlate well with weight loss outcomes and have been shown to diminish in both rodents and humans consuming low protein diets [15]. In addition, high levels of circulating BCAAs at baseline have also been directly linked to a heightened risk for cardiovascular diseases (CVDs). Although this harmful relationship may be counteracted by implementing a Mediterranean-style diet intervention to lessen the burden of pathophysiological processes and stimulate cardio-protective effects, BCAAs can apparently function as biomarkers to predict CVD outcomes, as well [13]. Because of BCAAs' great potential to function in the role of predictive biomarkers, their metabolic pathways may be able to serve as possible targets for the treatment of T2DM in the future [14].

BCAA metabolism is believed to be disrupted in other circumstances that typically involve IR, as well, such as liver and kidney dysfunction. However, despite the insulin resistant state, BCAA plasma levels in these conditions are still lower than in healthy subjects, which indicates that these organs may be involved in maintaining healthy BCAA blood concentrations

[1]. Furthermore, recent research studies have performed various investigations on BCAAs and IR, as well as on diabetes risks across different races, ethnicities, sexes, etc. They have been able to demonstrate the positive association between increased circulating BCAAs and IR in obese or diabetic patients. Nevertheless, these results are controversial, as they have shown notable discrepancies in BCAA levels depending on variations in ethnicities, races, sex, gene expressions, dietary patterns and distinct tissues. At the same time, there is a general dearth of studies focusing on innately "phenotypic and genetic factors" that could also have an influence on BCAA levels [7].

2.3. The Metabolism of BCAAs

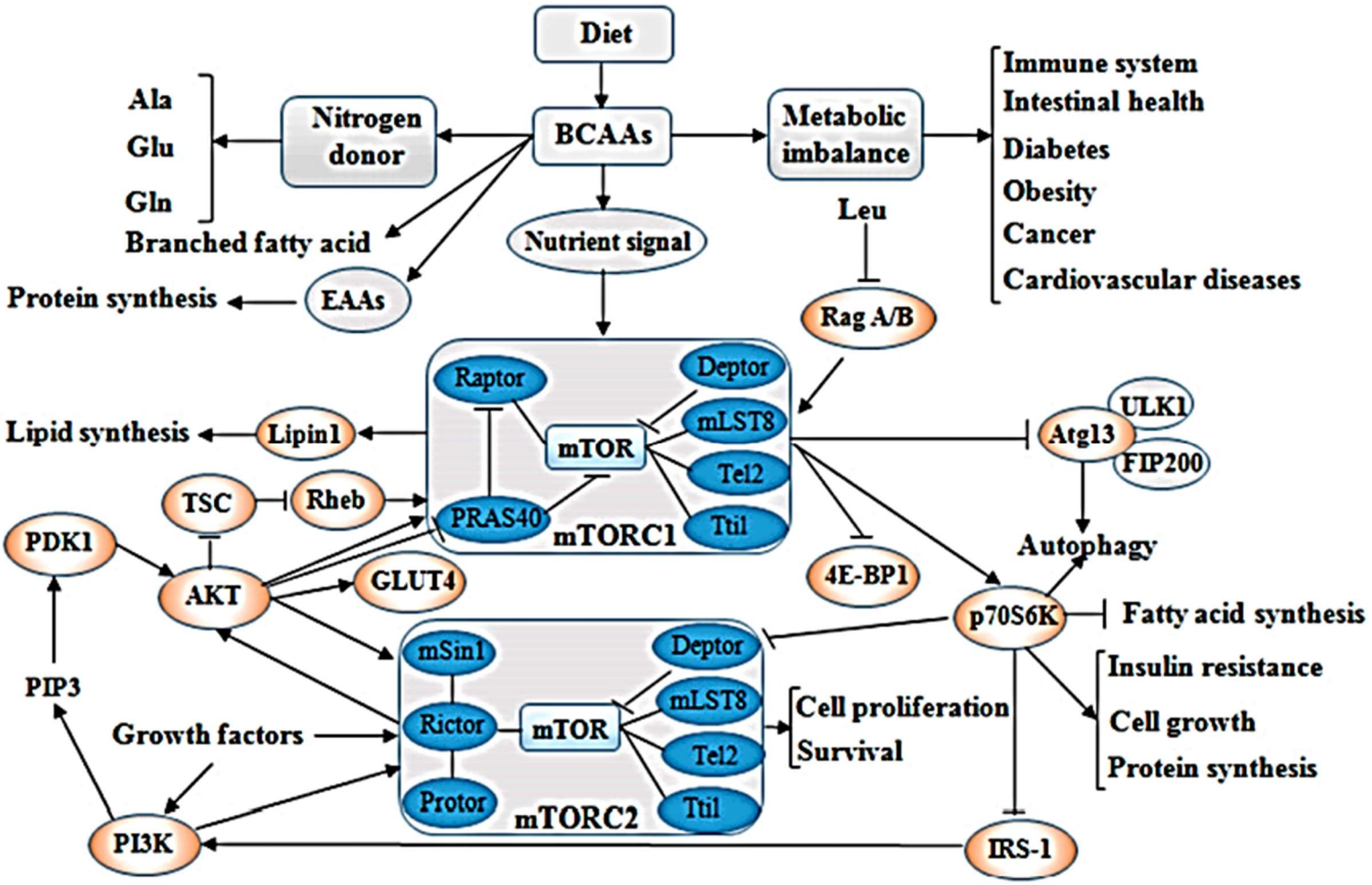
The catabolism of BCAAs is a complex process that requires multiple enzymatic steps, most of which take place in the mitochondria of cells after protein has been ingested [11, 17]. The first two steps of this catabolic pathway are the same for all three BCAAs [20]. However, unlike all other amino acids, which are primarily catabolized in the liver [19], the initial step of BCAA catabolism does not take place in the liver at all, and this is due to low hepatic activity of branched-chain-amino-acid aminotransferase (BCAT), which is the very first enzyme activated in the BCAA catabolism pathway [11]. The initial site of the majority of BCAAs' catabolic processes is located in skeletal muscle, because of high BCAT activity in these specific tissues [11]. The fact that BCAAs' first catabolic step entirely bypasses the liver for their primary catabolism to occur in the skeletal muscle makes BCAAs fairly unique, in comparison to other amino acids. In fact, approximately 50% of all amino acid uptake in the skeletal muscles consists of BCAAs, since leucine, isoleucine and valine are able to avoid "first pass metabolism." This metabolic concept refers to substrates being metabolized entirely by the liver immediately following their absorption from the intestine [17]. This bypass of first pass metabolism results in

BCAA concentrations rapidly increasing in systemic circulation, thus making them readily available to cells and tissues outside the liver. This phenomenon provides the BCAA-based nutritional formula with a distinct advantage, since these amino acids are much more efficient at targeting extrahepatic tissue, such as the brain and skeletal muscles, and can thus be oxidized in skeletal muscle itself [11, 19].

Research indicates that BCAAs may contribute to energy metabolism during exercise, in the form of both substrates and energy sources [19]; additionally, exercise not only significantly increases energy expenditure, but also substantially promotes the oxidation of BCAAs themselves [19, 20]. This is the case because exercise has an overall "profound effect" on protein metabolism: if a workout is intense enough, it will invariably result in a net loss of muscle protein, either due to high muscle breakdown, reduced protein synthesis, or even both at once. When this is happening, some amino acids – primarily BCAAs – are oxidized as a source of fuel, and byproducts of this oxidative process, such as ammonia, are produced in proportion to exercise intensity [20].

The particular extrahepatic metabolism of BCAAs has been identified as a significant factor in the pathophysiology of a variety of multi-faceted diseases, such as metabolic syndrome, cancer, and hepatic disease [7]. It is believed that impaired BCAA catabolism, especially in adipose tissue, contributes to the rise of BCAAs witnessed in obesity and in insulin resistant states [14]. Conversely, given the fact that skeletal muscle is the "largest site of glucose disposal," while also considering that loss of muscle mass may ultimately contribute to metabolic syndrome and T2DM, it seems possible that elevated circulating BCAA levels might actually *reduce* the risk of glucose intolerance and subsequent metabolic disease [3].

FIG. 5. This complex diagram illustrates BCAAs' balance & their multiple roles via the PI3K-AKT-mTOR signaling pathway. BCAAs play critical roles as nitrogen donors for several different amino acids, as well as nutrient signals in numerous metabolic functions through special signaling pathways, especially via the PI3K-AKT-mTOR pathway. BCAA metabolic imbalances may cause various health issues, such as diabetes & cancer [13].



Nie, C., He, T., Zhang, W., Zhang, G., & Ma, X. (2018).

III. TWO PERSPECTIVES ON BCAAS

An ongoing debate has been taking place surrounding the interplay of BCAAs, insulin resistance, and type 2 diabetes mellitus. Current evidence suggests that the metabolic effects of BCAAs can be either beneficial or detrimental with respect to the risk of T2DM, but neither effect has been established as an absolute in all cases. In other words, the metabolic effects of BCAAs are similar to that of a double-edged sword.

Research conducted on the effect of circulating serum BCAA concentrations and IR/insulin metabolism has demonstrated contradictory and somewhat controversial findings: while some studies indicate that impaired BCAA metabolism and increased plasma levels of BCAAs are associated with a higher risk for IR or hyperglycemia and subsequent T2DM, other studies demonstrate that increased plasma BCAA concentrations have no effect on insulin sensitivity whatsoever [12]. Some research has shown that close associations exist between BCAAs and plasma glucose levels, and it has also been widely demonstrated that BCAAs "upregulate glucose transporters and activate insulin secretion." Nonetheless, several researchers have proposed the notion that excessive BCAA intake could do more harm than good by contributing to the inhibition of insulin signaling [11]. The limited range of studies that have evaluated the association between dietary BCAA intake and the risk of T2DM have yielded similarly inconsistent results. One study claims that a higher intake of BCAAs is associated with a decreased risk of T2DM, while another study argues that high consumption of BCAAs does in fact increase the risk for development of T2DM [12]. Indeed, it appears that the effects of BCAAs are something of a double-edged sword.

This paradoxical role of BCAAs' impact on metabolism naturally raises some questions and concerns, especially when considering the fact that BCAAs are a popular nutritional

supplement for those who are active in the bodybuilding and fitness communities. Because BCAAs are most prominent for raising protein synthesis through the modulation of protein translation, they are especially appealing both to resistance and endurance athletes alike in their potential to aid with accelerated recovery, muscle hypertrophy, and lean body mass retention [3].

Despite the potentially beneficial associations between circulating BCAAs, improved cellular energetics, and increased skeletal muscle mass, elevated circulating BCAA levels have nonetheless been detected during metabolic pathologies that include IR and T2DM [3]. Yoon confirms that the perceived link between levels of circulating BCAAs, insulin resistant obesity, and T2DM has prompted speculation regarding whether BCAA levels can be viewed as a predictor for future IR or T2DM, in spite of the allegedly beneficial effects of a BCAA-rich diet and BCAA supplementation [6]. In light of the given information, there are two divergent perspectives on the topic of BCAAs and their impact on metabolic health:

a) increased plasma BCAAs are the *cause* of IR and T2DM, or

b) increased plasma BCAAs are the *result* of IR and T2DM, and can thus serve as effective biomarkers for metabolic risk.

Therefore, when looking at the big picture regarding BCAAs, it is important to consider whether these amino acids are in fact causative or predictive of IR, as well as what their potential role in insulin signaling may be [6]. It is also necessary to understand whether BCAA-rich diets are “harmful, helpful or neutral with respect to insulin and glucose homeostasis” [4, 6]. Based on already available data, consistent correlations do seem to exist between elevated circulating levels of BCAAs and metabolic disease in humans, especially in regards to IR [3]. Thus, it is crucial to identify accurate parameters or biomarkers that can most effectively reflect IR and

metabolic risks, in order to better understand the inherent mechanisms underlying obesity-related complications [7].

Lynch & Adams suggest that "perturbations in BCAA levels probably reflect the insulin resistant and T2DM 'pathophenotypes,' and BCAAs themselves are probably not necessary or sufficient to trigger disease" [4], although BCAA levels have been found to be elevated in the blood of obese, insulin resistant humans and rodents on more than one occasion [15]. As is the case with many different metabolites in the process of metabolic disease, such as glucose and lipids, BCAA accumulation does appear to correlate with and might have some predictive value of metabolic aberrations [3]. Consistent observations in cross-sectional and prospective human studies, along with limited other studies, have also suggested that BCAA supplementation actually leads to a "deterioration of insulin sensitivity" [4]. According to Yoon, elevated BCAA levels stimulate an intricate metabolic pathway involving a nutrient sensing complex, and this results in IR and other metabolic disorders [6]. It has also been hypothesized that elevated circulating BCAAs observed in an insulin resistant state may result from dysregulated BCAA degradation [3]. However, the results of recent investigations demonstrate that even in normal-weight subjects, a definitive association between increased blood levels of BCAAs and IR was detected, suggesting that perhaps the increased concentration of BCAAs found in obese subjects is likely related to IR itself, rather than obesity [1].

The idea that elevated levels of circulating BCAAs have a strong relation to metabolic disease, especially IR, is not necessarily under dispute. However, the interplay between circulating BCAAs and metabolic disease is indeed a highly complex process, so it has not yet been fully understood or analyzed. In fact, elevated circulating BCAAs may be a product of multiple factors [3]. Findings from the population-based cohort study conducted by Asghari et al.

on a sample of residents from a district of Iran's capital, Tehran, indicate that a high intake of BCAAs is indeed related to a greater risk of IR. In addition, out of the three BCAAs, a higher intake of leucine and valine, in particular, had a significant association with a higher risk for incident IR. Nevertheless, no major association was established between dietary BCAA intake and the development of hyperinsulinemia and pancreatic beta-cell dysfunction [12]. In fact, the direct influence of a particular diet on BCAA levels and subsequent IR is not yet recognized [7]. Gannon et al.'s findings agree with this notion, that despite being "essential" in nature, dietary protein intake does not appear to correlate with circulating BCAA levels. According to one of the reports on human studies that they summarized, it was clearly specified that while protein intake was linked with select amino acids (valine, phenylalanine, tyrosine, and glutamine), it was not in any way associated with actual IR. Consequently, it is believed that dysregulated BCAA catabolism may be the principal cause of elevated circulating BCAA concentrations observed in diabetics [3].

IV. DISCUSSION

It still remains unclear whether BCAAs are simply *markers* of the metabolic disturbances that ultimately lead to the development of T2DM, or if they are, at least in part, the actual *cause* of metabolic disturbances leading to T2DM. In other words, both the pros and cons of BCAAs must continue to be carefully weighed and thoroughly analyzed. Gannon et al. propose two alternative theories: Under more or less "ideal" conditions of metabolic homeostasis or energy deprivation, BCAAs – and leucine in particular – may be capable of supporting improved "metabolic phenotypes," while also promoting beneficial metabolic properties such as greater mitochondrial content, better insulin sensitivity and glucose uptake, and increased muscle

preservation. However, under conditions of "chronic excess energy," cells – especially adipocytes – seem to lose their ability to efficiently degrade BCAAs, which can subsequently lead to an accumulation of BCAAs and related metabolites, both intracellularly and in overall circulation [3].

Irrespective of any theories, there remains a dearth of knowledge regarding the full potential of BCAAs, as well as their complete impact on pathways of metabolism that affect pancreatic alpha-cell function [14]. Additionally, hypotheses surrounding BCAAs and their effects on metabolic outcomes are still shrouded with speculation. Considering the vast diversity and varied possibilities of experimental models, which can range from basic cell lines to actual animal studies, plenty of discrepancies still abound in the literature – for instance, in many cell studies that have been described so far, amino acid concentrations in the cells are often in substantial excess of AA concentrations that are physiologically attainable in mammals [3]. Further investigation is still required to better understand the variable reports on all of BCAAs' impacts, ranging from improving glucose utilization to inducing IR [11]. This is especially true because current experiments are scientifically sound, but they are nonetheless far removed from reality – in other words, the context in which humans typically consume BCAAs, both in terms of their amounts and sources. This is compounded even more when considering the vast array of behaviors and food chemicals with which BCAAs are usually consumed [3].

To date, no large-scale population-based studies investigating the relationship between dietary BCAA intake, the risk of IR and pancreatic beta-cell dysfunction have been conducted, either [12]. Moreover, despite many years of ongoing research, the exact mechanisms linking IR and obesity-related metabolic complications also have yet to be fully established and understood [7]. Furthermore, much of the effects of BCAAs appear to manifest themselves on an

individualized, case-by-case basis. Based on much of the data that currently exists, it appears that BCAAs' influences on health and metabolism are primarily dependent upon experimental model, energy equilibrium, and tissue type [3]. For instance, elevated BCAA levels and their connection with IR appear to be race-dependent, at least to some extent. Zhao et al. advise that it would be ideal for future research studies to extend their sample sizes to include subjects of different races, in order to better validate the varied findings on BCAAs. In regards to gender differences, many studies indicate that obese men display higher BCAA levels and a stronger positive correlation with IR compared to female test subjects [7]. According to one of the human studies reports summarized by Gannon et al., individual BCAAs exhibited "sex- and obesity-dependent associations," and additionally, they specifically required abdominal obesity to be present in women to exert a tangible metabolic effect [3]. Meanwhile, in the "Young Finn's Study," BCAAs were directly linked with IR in men but not in women, and several other amino acids showed no association with IR whatsoever [21]. This suggests that future studies should consider gender differences more carefully in the process of study design and data analysis. Zhao et al. confirm that diverse racial profiles and gender differences – and even genetics – can have substantial effects on BCAA levels and IR, so these variables should also be accounted for by conducting research with larger and more diverse study populations [7].

Gannon et al. echo this sentiment, concurring that the role individual BCAAs play in the development of IR remains unclear, based on all the data that already exists. It is possible that excess intake of calories in general, coupled with excessive lipid consumption and elevated fat mass in the body, may contribute to the initial onset of metabolic dysregulation, which in turn leads to greater BCAA accumulation. This hypothesis is supported by the fact that many athletic populations tend to consume excess protein and/or BCAAs, yet they do not go on to develop IR

or other metabolic diseases [3]. What's more, the role of obesity during the process of BCAA accumulation is not apparent in all populations. Likewise, the accumulation of circulating BCAAs is not detected in every experimental model of obesity, but this may be due to differences among the experimental models themselves. Nonetheless, the accumulation of BCAAs during severe IR is a fairly consistent observation, although based on existing research interpretations, it seems as though "depressed BCAA catabolic enzymes" may very well be a contributing factor in the accumulation of BCAAs, and may thus be altered by energy balance [3]. Shimomura et al. note that more follow-up studies on BCAAs are necessary on several other fronts. The most effective ratio for consuming the three BCAAs in a way that allows to reap all their benefits remains unknown. As they point out, a variety of interesting observations have been made on BCAAs, but future studies should be designed with the intention of clarifying the mechanisms responsible for their positive post-workout effects, as well as identifying the proportion in which each BCAA should be consumed to maximize their collective exercise-boosting properties. [19].

V. CONCLUSION

Considering the assortment of data that is currently available, it may be safe to surmise that the effect of dietary BCAAs on T2DM risk most likely hinges on sex and individual states of energy balance. Perhaps the real issue in many cases isn't so much the "fault" of BCAAs themselves, but rather, different individuals' pathologically-prone metabolic backgrounds. It is possible that BCAAs aren't truly the cause of metabolic abnormalities, but their accumulation is simply one of the consequences of a metabolism that is already ailing due to many other more severe health factors.

For example, given ample data both from health and athletic populations, it appears that dietary sources of BCAAs are unlikely to be "independently sufficient" to actually cause metabolic disease in "otherwise healthy" populations. In other words, BCAAs and overall protein consumption on their own are incapable of independently spurring the onset of metabolic disease plus the dysregulated BCAA metabolism associated with it [3]. It's also possible that other metabolic and health factors might align more closely with elevated BCAAs than IR or T2DM. For instance, obesity may track more strongly with elevated BCAAs than either T2DM or metabolic syndrome. In a study conducted with 1,302 participants ages 40-79, higher BCAA levels went hand in hand with male sex, older age and metabolic syndrome, as well as with obesity, hypertension, dyslipidemia, cardiovascular risk and uric acid [21]. This further underscores the depth of complexity of elevated BCAAs as a metabolic marker, as well as just how many other factors are entwined with this one.

In spite of gaps in the literature, Zhao et al. contend that BCAAs can be used as a valuable biomarker of IR, as well as a potent predictor for T2DM risks down the line. Apart from reflecting an insulin resistant state, BCAAs may also provide feedback regarding various pharmacological effects of drug interventions. Thus, they could serve as a useful biomarker to help monitor for an early response to therapeutic interventions in T2DM patients. Regularly measuring BCAA levels might also help more effectively capture the entire course of disease progression, beginning with obesity and crossing into IR, T2DM and subsequent efficacy of drug treatments [7].

As Yoon and Holeček concluded in their respective reviews, whether elevated BCAA levels are merely markers of IR or a dysfunctional metabolism, or if they actually contribute to IR and other metabolic abnormalities remains an uncertainty for the time being, but this topic is

progressively gaining traction and attracting more research interest [6, 11]. With this in mind, the entire scope of BCAAs' potential impacts and effects on metabolic health should undoubtedly be determined well in advance, prior to making any health-oriented decisions to use them on obese subjects and patients with T2DM [11].

REFERENCES

[1] Adeva, M. M., Calviño, J., Souto, G., & Donapetry, C. (2011). Insulin resistance and the metabolism of branched-chain amino acids in humans. *Amino Acids, 43*(1), 171-181. doi:10.1007/s00726-011-1088-7

[2] Czech M. P. (2017). Insulin action and resistance in obesity and type 2 diabetes. *Nature medicine*, *23*(7), 804–814. https://doi.org/10.1038/nm.4350

[3] Gannon, N. P., Schnuck, J. K., & Vaughan, R. A. (2018). BCAA Metabolism and Insulin Sensitivity - Dysregulated by Metabolic Status? *Molecular Nutrition & Food Research, 62*(6), 1700756. doi:10.1002/mnfr.201700756

[4] Lynch, C. J., & Adams, S. H. (2014). Branched-chain amino acids in metabolic signaling and insulin resistance. *Nature Reviews Endocrinology, 10*(12), 723-736. doi:10.1038/nrendo.2014.171

[5] Sangwung, P., Petersen, K. F., Shulman, G. I., & Knowles, J. W. (2020). Mitochondrial Dysfunction, Insulin Resistance, and Potential Genetic Implications: Potential Role of Alterations in Mitochondrial Function in the Pathogenesis of Insulin Resistance and Type 2 Diabetes. *Endocrinology, 161*(4), 1-10. doi:https://doi.org/10.1210/endocr/bqaa017

[6] Yoon, M. (2016). The Emerging Role of Branched-Chain Amino Acids in Insulin Resistance and Metabolism. *Nutrients, 8*(7), 405. doi:10.3390/nu8070405

[7] Zhao, X., Han, Q., Liu, Y., Sun, C., Gang, X., & Wang, G. (2016). The Relationship between Branched-Chain Amino Acid Related Metabolomic Signature and Insulin Resistance: A Systematic Review. *Journal of Diabetes Research, 2016*, 1-12. doi:10.1155/2016/2794591

[8] Andrews, R. (2019, December 30). All About BCAAs. Retrieved from https://www.precisionnutrition.com/all-about-bcaas

[9] Mayo Clinic Staff. (2020, August 26). Type 2 diabetes. Retrieved from https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/symptoms-causes/syc-20351193

[10] Petre, A. (2016, November 25). BCAA Benefits: A Review of Branched-Chain Amino Acids. Retrieved from https://www.healthline.com/nutrition/bcaa

[11] Holeček, M. (2018). Branched-chain amino acids in health and disease: Metabolism, alterations in blood plasma, and as supplements. *Nutrition & Metabolism, 15*(1). doi:10.1186/s12986-018-0271-1

[12] Asghari, G., Farhadnejad, H., Teymoori, F., Mirmiran, P., Tohidi, M., & Azizi, F. (2018). High dietary intake of branched-chain amino acids is associated with an increased risk of insulin resistance in adults. *Journal of Diabetes, 10*(5), 357-364. doi:10.1111/1753-0407.12639

[13] Nie, C., He, T., Zhang, W., Zhang, G., & Ma, X. (2018). Branched Chain Amino Acids: Beyond Nutrition Metabolism. *International Journal of Molecular Sciences, 19*(4), 954. doi:10.3390/ijms19040954

[14] Chen, X., & Yang, W. (2015). Branched-chain amino acids and the association with type 2 diabetes. *Journal of Diabetes Investigation, 6*(4), 369-370. doi:10.1111/jdi.12345

[15] Cummings, N. E., Williams, E. M., Kasza, I., Konon, E. N., Schaid, M. D., Schmidt, B. A., . . . Lamming, D. W. (2018). Restoration of metabolic health by decreased consumption of branched-chain amino acids. *The Journal of Physiology, 596*(4), 623-645. doi:DOI: 10.1113/JP275075

[16] Centers for Disease Control and Prevention. (2020, February 18). A Snapshot: Diabetes In The United States. Retrieved from https://www.cdc.gov/diabetes/library/socialmedia/infographics/diabetes.html

[17] Cole, J. T. (2015). Metabolism of BCAAs. *Branched Chain Amino Acids in Clinical Nutrition: Volume 1, Nutrition and Health, 1*, 13-24. doi:10.1007/978-1-4939-1923-9_2

[18] Hales, C., Carroll, M., Fryar, C., & Ogden, C. (2020, February 27). Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. Retrieved from https://www.cdc.gov/nchs/products/databriefs/db360.htm

[19] Shimomura, Y., Murakami, T., Nakai, N., Nagasaki, M., Harris, R.A. (2004). Exercise Promotes BCAA Catabolism: Effects of BCAA Supplementation on Skeletal Muscle during Exercise, *The Journal of Nutrition, 134*(6), 1583S–1587S. https://doi.org/10.1093/jn/134.6.1583S

[20] Negro, M., Giardina, S., Marzani, B., & Marzatico, F. (2008). Branched-chain amino acid supplementation does not enhance athletic performance but affects muscle recovery and the immune system. *The Journal of sports medicine and physical fitness*, *48*(3), 347–351.

[21] Bloomgarden Z. (2018). Diabetes and branched-chain amino acids: What is the link? *Journal of diabetes*, *10*(5), 350–352. https://doi.org/10.1111/1753-0407.12645