Nutrition and Health
Series Editor: Adrianne Bendich

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Vinood B. Patel *Editors*

Branched Chain Amino Acids in Clinical Nutrition

Volume 1

Humana Press

Nutrition and Health

Adrianne Bendich, Ph.D., FASN, FACN, Series Editor

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Preface

In man, the branched chain amino acids (leucine, isoleucine, and valine) are essential amino acids and thus must be obtained from dietary components. The branched chain amino acids are not only necessary for the synthesis of proteins but also have other metabolic functions and roles. For example, over several decades' evidence has supported the notion that branched chain amino acids, particularly leucine, are important in ameliorating or restoring metabolic imbalance. Studies in the 1970s showed that leucine promoted protein synthesis in muscle in vitro. Later, in the 1980s, it was shown that the branched chain amino acids stimulated protein synthesis in vivo. Subsequently, studies showed that branched chain amino acids could potentially be used clinically in ameliorating muscle catabolism. More recently the branched chain amino acids have been added to performance-enhancing supplements. Although this is a simplistic synopsis of historical events, it is now evident that the branched chain amino acids have a variety of functions. In simple terms the knowledge base associated with the branched chain amino acids have now been successfully harvested to enhance human health. Branched chain amino acids, like some other amino acids, have an almost ubiquitous function and are important in maintaining the cellular milieu of virtually every organ in the human body. For example, branched chain amino acids have roles in carbohydrate and lipid metabolism, insulin release and resistance, proteolysis, formation of keto acids, obesity prevention, and cancer. This does not mean to say that branched chain amino acids are the universal panacea. Indeed the administration of high amounts of branched chain amino acids may be toxic. The science of branched chain amino acids is complex and finding all the relevant information in a single source has hitherto been problematic. This is, therefore, addressed in *Branched Chain Amino Acids in Clinical Nutrition.*

The book has seven major Parts in two volumes.

Volume I

Part I: Basic Processes at the Cellular Level
Part II: Inherited Defects in Branched Chain Amino Acid Metabolism
Part III: Experimental Models of Growth and Disease States: Role of Branched Chain Amino Acids

Volume II

Part I: Role of Branched Chain Amino Acids in Healthy Individuals
Part II: Branched Chain Amino Acids: Status in Disease States
Part III: Branched Chain Amino Acids and Liver Diseases
Part IV: Branched Chain Amino Acid Supplementation Studies in Certain Patient Populations

Coverage includes the individual branched chain amino acids, amino acid ratios, essential amino acids, metabolism, amino acids cocktails, aminotransferases, tRNA, PPAR, uncoupling proteins,

insulin and insulin resistance, glucose and glycemic control, the hypothalamus, sirtuin, ammonia, cirrhosis, encephalopathy, apoproteins, maple syrup urine disease and oxidation disorders, mental retardation, fetal growth, skeletal and cardiac muscles, muscular dystrophy, amyotrophic lateral sclerosis, anorexia, obesity and weight loss, bladder carcinogenesis, tolerability, recovery, exercise, functional adaptations, psychomotor performance, whey protein, brain injury, obstructive pulmonary disease, ethanol oxidation, albumin, late evening snacks, organ transplantation, quality of life, and skin and radiotherapy. Finally there is a chapter on web-based material and additional reading.

Contributors are authors of international and national standing, leaders in the field, and trendsetters. Emerging fields of science and important discoveries are also incorporated in *Branched Chain Amino Acids in Clinical Nutrition.*

This book is designed for nutritionists and dietitians, public health scientists, doctors, epidemiologists, health care professionals of various disciplines, policy makers, and marketing and economic strategists. It is designed for teachers and lecturers, undergraduates and graduates, and researchers and professors.

London, UK

Rajkumar Rajendram
Victor R. Preedy
Vinood B. Patel

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science; (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields; (3) extensive, up-to-date fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overlap of information between chapters, but targeted, interchapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient as well as health professional questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Branched Chain Amino Acids in Clinical Nutrition, a two-volume book, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, is a very welcome addition to the Nutrition and Health Series and fully exemplifies the Series' goals. The first volume of *Branched Chain Amino Acids in Clinical Nutrition*, "Cellular Processes, Genetic Factors and Experimental Models of Branched Chain Amino Acid Functions and Metabolism," is organized into three relevant parts. The ten introductory chapters in the first part, entitled "Basic Processes at the Cellular Level," provide readers with the basics so that the more clinically related chapters can be easily understood. The first chapter provides a broad-based perspective on the protein requirements for humans and describes the 20 amino acids that are classified as essential for humans to consume as these cannot be synthesized de novo in the human body. Tables and figures included describe major food sources of essential amino acids and specific food sources of branched chain amino acids. The second chapter describes the structures and functions of the three branched chain amino acids, leucine, isoleucine, and valine, that are classified as essential amino acids. We learn that these three branched chain amino acids make up approximately one third of all the amino acids in the body. The majority of the three amino acids are found in skeletal muscle where these function as both structural elements and stores for systemic nitrogen. The dietary requirements are approximately 40, 20, and 19 mg/kg of body weight/day of

leucine, valine, and isoleucine, respectively. Excellent sources of these amino acids are red meat, dairy, and soy protein-containing products. The typical Western diet provides sufficient protein to normally assure consumption of adequate levels of branched chain amino acids. The enzymes involved in the catabolism of these amino acids are described in detail and their locations within the body are reviewed with emphasis on their roles in muscle and the brain. The third chapter provides more detailed descriptions of the 15 enzymes responsible for the transamination and metabolism of the individual branched chain amino acids and describes the enzymatic reactions that share the same enzymes as well as those that differ in the metabolism of these amino acids. Peripheral as well as brain enzyme systems and shuttles are described in detail and illustrated in the included figures.

Chapter 4 describes in detail the role of isoleucine specifically in the functioning of certain adipocytes as well as its function in glucose metabolism. Laboratory animal studies are reviewed and the importance of isoleucine in the activation of liver and skeletal muscle free fatty acid uptake and oxidation is linked to a potential role in the development of obesity. The fifth chapter describes the unique metabolic activities of leucine. Leucine has been found to be a potent activator of the mammalian target of rapamycin (mTOR) pathway which is a critical nutrient-sensing pathway that governs cell metabolism, cell growth, and proliferation. Leucine also has a role in regulating insulin secretion and glucose utilization. The chapter includes an in-depth investigation of leucine regulation of several critical cellular processes in pancreatic β-cells, including metabolism, growth, proliferation, and insulin secretion, which ultimately influence overall glucose homeostasis. The multiple routes that are involved in acute regulation of insulin secretion are illustrated in the included figures.

Chapter 6 looks at the data from laboratory animal experiments that examine the effects of leucine and isoleucine on glucose metabolism and insulin regulation. These three chapters provide a comprehensive review of the roles of these amino acids in energy metabolism and suggest that this is an area where well-controlled clinical studies are needed. The seventh chapter provides additional detailed information concerning the importance of the hypothalamic metabolism of leucine in the brain and its effects on liver glucose production. The eighth chapter reviews new studies in cell culture and laboratory animals that are exposed to leucine and resveratrol. The rationale for this combination is that both leucine and resveratrol stimulate sirtuin-dependent pathways that are linked to enhancing longevity. The authors describe the synergistic actions of both substances on sirtuin-dependent downstream metabolic effects.

The next chapter in this part describes the role of branched chain amino acids in the metabolism of ammonia. This is a complex area of basic as well as clinical investigation and both are well described in this chapter. The author also describes the open questions concerning the interactions between muscle and liver metabolism of ammonia and the potential for unexpected effects when branched chain amino acids are given therapeutically. The last chapter in this part, Chapter 10, describes the use of a stable isotope form of leucine to calculate the in vivo rates of synthesis and catabolism of lipoproteins that are important in the determination of cardiovascular risk, survival of HIV, and other clinical manifestations of abnormal lipoprotein levels. This detailed chapter describes the calculations required to determine in vivo circulating HDL, VLDL, and LDL levels without exposing the patient to radiation.

Part II contains four chapters that review the inherited defects in branched chain amino acid metabolism and describes the resultant inborn errors of metabolism. The first chapter in this part focuses on genetic defects in the oxidative pathways involved in the breakdown of valine, leucine, and isoleucine. We learn that there are a total of 15 different enzyme reactions that are required for the breakdown of valine, leucine, and isoleucine. The chapter focuses on the 11 genetic defects and the enzymatic consequences of 11 of the pathways. Descriptions of the pathophysiological changes that are seen with each of the amino acid's associated genetic mutations in critical enzymes are described. Maple sugar urine disease is the most common manifestation of errors in the coding of the catabolic enzymes involved in the decomposition of the three branched chain amino acids and results in higher than normal levels of the amino acids in the blood and urine. Chapter 12 describes in detailed text and tables the 202 mutations described in 2013 that are associated with maple sugar urine disease. Because

of the rapid onset of severe brain damage in neonates with this disease, newborn screening is done on all infants in the USA and in many other parts of the world. Clinically, treatments involve the provision of a diet low in branched chain amino acids. There is ongoing research concerning the biochemical mechanisms associated with the clinical presentations of the many of the genetic defects associated with this disease. Chapter 13 describes other adverse consequence of genetic mutations specifically to the isoleucine degradation enzymes. The authors have documented cases of mental retardation, motor dysfunctions, behavioral disorders, and other abnormal manifestations of physical and mental functions in children and young adults that carry these mutations. The X-linked inborn errors of isoleucine degradation are described in detail and the author clearly indicates the need for further research. The next chapter examines the results of laboratory animal studies that look at the effects of a genetic defect in the metabolism of valine and the consequences to eating behaviors. The authors posit that the resultant valine deficiency specifically can affect satiety centers in the brain resulting in anorexia. Translating this research into clinical studies has not as yet occurred.

Part III: Experimental Models

Part III includes seven chapters that describe laboratory studies with experimental models of growth and certain disease states where branched chain amino acids have been examined to determine the metabolic role of these amino acids; in several chapters the administration of one or all of the branched chain amino acids has been shown to provide some improvement. Chapters 15 and 16 review the importance of protein and specific amino acids in the growth of the fetus (Chapter 15) and the neonate (Chapter 16). Intrauterine growth retardation is associated with a reduction in organ growth and permanent changes in organ metabolism and/or structure. As discussed by the author, intrauterine growth retardation (IUGR) may result from maternal undernutrition that can increase the risk of lifelong adverse health effects. Experimental models have provided data indicating that IUGR causes changes in islet cells, in the hypothalamic-pituitary-adrenal axis, and in the secretion of prolactin, progesterone, estradiol, and insulin, as well as in the glucose uptake by muscles, body fat content, and mitochondrial function. IUGR increases the risk of cardiovascular diseases, diabetes, and obesity in adult life. IUGR causes a reduction in organ growth and permanent changes in organ metabolism and/or structure. The experimental models have shown that leucine supplementation in models of low protein intake may not be as valuable as increase in total protein intake. The chapter includes excellent tables and figures. Chapter 16 provides unique data from a neonatal pig model on the role of leucine in muscle metabolism. The authors have used parenteral leucine infusions and show that a physiological rise in leucine enhances protein synthesis in skeletal muscle and cardiac muscle. They have also shown that leucine supplementation of a meal acutely stimulated protein synthesis in the neonatal pig model. Two chapters examined the importance of branched chain amino acids in models of obesity. Chapter 17 reviews the data from rodent models concerning the effects of branched chain amino acid status on insulin resistance and alterations in adipose tissue. Chapter 18 examines the data from models of high fat intake that have shown that leucine functions as a nutrient signal to coordinately regulate three major signaling pathways in the liver, skeletal muscle, and adipose tissue. Dietary supplementation of leucine significantly ameliorated the deleterious effects of consumption of a high-fat diet including obesity, hepatic lipid accumulation, mitochondrial dysfunction, and insulin resistance. The metabolic benefits of leucine supplementation included upregulation of genes related to mitochondrial synthesis of critical enzymes, increases in metabolic rates, and suppression of inflammation in adipose tissue.

The last three chapters in this part discuss different models that reflect the functions of branched chain amino acids. Chapter 19 describes research underway to understand the etiology of amyotrophic lateral sclerosis (ALS), an adult-onset neurodegenerative disease, also known as Lou Gehrig

disease, that is characterized by degeneration of neurons in the brain and spinal cord leading to progressive paralysis of respiratory and limb muscles. Both in vitro and laboratory animal studies are reviewed. There are indications of adverse effects of branched chain amino acids in certain of the models as a result of neurotoxicity that may be linked to oxidative stress. At present it is not known if these effects would be seen in humans, but caution is urged. The next chapter provides a unique perspective on the potential for leucine to enhance ethanol metabolism in the liver. The author describes experiments showing that leucine specifically (and not valine) accelerates ethanol clearance after acute ethanol administration by enhancing alcohol-metabolizing enzyme activities. Leucine treatment before alcohol intake also enhanced alcoholic enzyme activities and accelerates ethanol metabolism. It is well recognized that chronic alcohol intake leads to liver failure, such as hepatic inflammation and fatty liver, and induces liver cirrhosis. Accelerating ethanol oxidation may prevent liver failure. The last chapter in this part describes the development of a two-stage model of bladder cancer that involves the use of known cancer initiators and promoters. In this model, branched chain amino acid supplementation at very high doses compared to normal human dietary intakes enhanced tumor formation when certain basal diets were fed, but not with others. As indicated by the authors, "To date, however, there is no epidemiological data relevant to a relationship of dietary BCAA with the risk of bladder cancer."

Volume II

The second volume of *Branched Chain Amino Acids in Clinical Nutrition* concentrates on the role of these amino acids in healthy individuals, the effects of certain diseases on branched chain amino acid status, and finally, data from clinical studies that included therapeutic use of the amino acids in patients.

Part I: Role of Branched Chain Amino Acids in Healthy Individuals

The first part contains five chapters that begin with an in-depth examination of the safety of leucine supplementation in healthy adults. Often healthy adults use leucine supplements when they are exercising or attempting to build muscle. The next three chapters review the effects of leucine on muscle. The last chapter in the Part describes the potential for optimal surgery outcomes when amino acid ratios are used as an index of protein status. Chapter 1 describes the process used by the authors to determine the tolerable, and presumably safe, upper limit of intake of leucine in healthy adults. They define this value as the point at which the metabolic capacity to catabolize or oxidize the excess amino acid is exceeded because it represents the intake where the normal regulatory mechanisms are no longer sufficient to dispose of the excess. The amino acid intake corresponding to this inflection point does not represent a toxic intake level, but rather suggests that with increasing dietary intakes above this level the potential or risk for adverse events will increase. Also, amino acid intakes above this point are usually characterized by an increasing rate of accumulation in blood and excretion of the amino acid, and its secondary catabolites in urine. The figures included in this chapter help to illustrate these relationships. The experimental design used for leucine is reviewed and the authors report that with increasing intakes of leucine, a dose–response in leucine oxidative capacity was observed, with a breakpoint estimated at 550 mg/kg bw/day or 39 g/day for a 70 kg healthy adult. Simultaneous and significant increases in blood ammonia concentrations, plasma leucine concentrations, and urinary leucine excretion were observed with leucine intakes higher than 500 mg/kg bw/day. Thus, under acute dietary conditions, intakes greater than 500 mg leucine/kg bw/day may potentially increase the risk of adverse events, and is proposed as the tolerable upper safe intake (UL) for leucine in healthy adults.

The next chapter examines the requirements for protein and leucine intake in elite athletes to support skeletal muscle regeneration processes following endurance exercise in trained skeletal muscle. The authors present their rationale for adding free leucine to dietary protein to enhance the combined exercise-nutrient muscle response to the post-exercise regenerative processes and protein synthesis. Both the high dose (70 g whey protein/15 g leucine) and low dose (23 g whey protein, 5 g leucine) co-ingested with carbohydrate and fat over the first 90 min following intense cycling resulted in a proinflammatory transcriptome associated with increased leukocytes that reverted by 240 min to an anti-inflammatory signal in skeletal muscle. The other measurements also pointed to a positive effect of the post-exercise supplementation; however, in addition to the acute studies, long-term studies in trained athletes are needed. Chapter 3 reviews studies that used whey protein (from milk) plus leucine. The doses of L-leucine used in the studies reviewed varied from 2.24 to 7.5 g while the whey protein doses varied from 6.7 to 25 g. Outcomes also varied and included muscle responses post-exercise, in different aged populations and immune functions following exercise. The authors suggest that future studies assess dietary intakes and use consistent outcomes. The next chapter in this part reviews the data linking muscle atrophy in patients caused by several diseases to metabolic rationales for administering branched chain amino acids. The authors describe both animal models and patients with cancer-induced muscle loss (cachexia), glucocorticoid-induced muscle atrophy from Cushing's syndrome, as well as long-term therapeutic use of glucocorticoids, sarcopenia, and sepsis-induced muscle protein degradation. The final chapter, Chapter 5, describes the use of a ratio of branched chain amino acids to tyrosine as an index of presurgery health in patients with liver cancer; the index can also help to identify patients who would benefit with amino acid supplementation post surgery. Liver cancer patients undergoing surgical resection who had a low ratio before surgery had significantly more complications as well as more severe complications than patients with higher ratios. The authors suggest that liver cancer patients who have higher albumin levels (indicative of better liver function) and also have a higher ratio are at reduced risk for postsurgery complications. Patients with high albumin levels and low ratio may be the best candidates for supplementation with branched chain amino acids postsurgery.

Part II: Branched Chain Amino Acids: Status in Disease States

Part II contains five chapters that examine diseases of the heart, brain, and lungs and how these diseases affect the branched chain amino acid status of the patient. Branched chain amino acids, as discussed above, are critical for skeletal muscle integrity and are a major site of these amino acids' metabolism. Their role in cardiac muscle is the topic of Chapters 6 and 7. Chapter 6 examines clinical manifestations of genetic defects in branched chain amino acid metabolism as seen in propionic acidemia and methylmalonic acidemia that have been associated with dilated and hypertrophic cardiomyopathies. In addition to genetically related changes in branched chain amino acid metabolism, alterations in their metabolism are also seen in heart failure patients independent of a genetic cause. This is a new area of clinical research and a number of metabolic paths involving the catabolism of branched chain amino acids are hypothesized to potentially adversely affect cardiac tissue. Another new area that links branched chain amino acids with heart function, reviewed in Chapter 7, is the complex outcomes of mitochondrial cardiomyopathies (MCM) produced by mutational defects in energetic metabolism. Specifically, a mutation involving the branched chain amino acid valine has been identified and linked to impaired heart functions in the neonates that inherit this defect.

The next two chapters examine the effects of branched chain amino acids on brain functions, first as related to psychomotor skills and, in Chapter 9, their role in traumatic brain injury. With regard to psychomotor skills, we learn that these coordinated actions are used in everyday life, occupational work, and sport activities. Psychomotor performance depends mainly on cognitive function, attention,

concentration, and decision-making. Branched chain amino acids, especially leucine, can cross the blood–brain barrier and influence these functions through their involvement in the synthesis of neurotransmitters. Ingestion of small doses of branched chain amino acids has been shown to improve psychomotor performance. However, higher doses can exert negative effects on some brain functions and may impair psychomotor performance. New research is underway to better understand the biochemical changes in the brain following traumatic brain injury. Clinical research has reported that immediately following the brain injury, there are phase-dependent changes in plasma amino acids with a different profile in the acute, subacute, and rehabilitation phase. During the acute phase, decreased plasma branched chain amino acid levels are associated with increased plasma aromatic amino acid concentrations. There are numerous other changes in the brain and the authors of Chapter 9 indicate that currently, it is not known if repletion of the branched chain amino acids is of benefit immediately or will be of more value during a different phase of recovery. The last chapter in this section reviews the effects of chronic obstructive pulmonary disease (COPD) on branched chain amino acid status and the potential to enhance the strength of these patients with nutritional addition of these amino acids. The authors point out that COPD patients with low body mass index (BMI) and/or severe airflow limitations exhibit reduced branched chain amino acid profiles, but those with a normal BMI and/or moderate airflow limitations do not. Nevertheless, both muscle and plasma levels of the amino acid levels are directly related to the levels of muscle wasting seen in patients with COPD.

Part III contains five chapters that examine the influence of branched chain amino acids in patients with liver diseases. Chapter 11 describes the effects of liver disease on branched chain amino acid status and then reviews the use of the amino acids as therapeutic supplements in patients with liver cirrhosis, liver cancer, and additional adverse consequences of liver disease. In patients with liver cirrhosis, levels of branched chain amino acids are decreased in the blood and the levels of aromatic amino acids and methionine are increased. The authors examine in depth the adverse effects of these changes on brain and muscle biochemistry and by using global gene expression analysis, the authors provide critical data on the molecular mechanisms by which hepatic damage can be reversed following branched chain amino acid supplementation. The next chapter discusses the importance of the liver in the synthesis of albumin. Albumin is the major protein produced in the liver and albumin represents over 50% of the total plasma proteins. Plasma albumin level is a standard index of nutritional status, liver function, and/or pathophysiological conditions. One of the most important factors regulating plasma albumin levels is ingestion of a protein-rich meal. The authors indicate that in Japan, pharmacological supplementation of branched chain amino acids is used to improve hypoalbuminemia in patients with liver cirrhosis. The chapter focuses on the effects of amino acid supplementation, including branched chain amino acids, on the regulation of albumin synthesis and provides excellent figures to help the reader. Chapter 13 describes the effects of liver cirrhosis caused by hepatitis C and nonalcoholic fatty liver disease and the consequent protein energy malnutrition and muscle wasting that can accompany these serious liver diseases. The author indicates that these major metabolic defects result in a state of starvation during the overnight sleep time and provides clinical evidence of the benefits of a nighttime snack that includes branched chain amino acids. Based upon the preliminary findings, it is suggested that well-controlled studies be undertaken.

The next chapter reviews the importance of stabilizing the nutritional status in patients with end-stage liver disease requiring liver transplantation. Accurate nutritional assessment and adequate perioperative nutritional treatment are essential for improving outcomes after liver transplant. The overall survival rate in patients with low skeletal muscle mass was found to be significantly lower than in patients with normal/high skeletal muscle mass. The authors report that perioperative nutritional therapy including branched chain amino acids is useful for patients with sarcopenia, whose prognosis is poor without nutritional therapy. The final two chapters in this part review the importance of branched chain amino acid supplementation in the treatment of the post-liver surgery patient. In Chapter 15, we learn that post-transplant bacteremia is one of the most serious complications following liver transplantation. One potential avenue for prevention of bacteremia that is being tested is nutritional

support. It is known that in patients who have not been given supplementation prior to transplantation, serum levels of branched chain amino acids generally decrease and have been reported to be a risk factor for post-transplant bacteremia. This chapter reviews previous studies on the beneficial effects of branched chain amino acid supplementation in liver transplant patients: prevention of bacteremia, potential mechanisms of action, and avenues for future research. Chapter 16 examines the effects of liver surgery as a result of liver cancer and the data suggesting that branched chain amino acid supplementation may enhance the prognosis of these patients. The authors indicate that most liver cancers occur in patients with chronic liver disease. Advances in surgical technology and perioperative management have led to the standard use of hepatic surgical procedures for liver cancer and also metastatic liver tumors. Branched chain amino acid supplementation improves postoperative quality of life over the long term after hepatic resection by restoring and maintaining nutritional status and whole-body kinetics.

The last part in volume II examines the use of branched chain amino acid supplementation in several different patient populations that further attests to the growing interest in the clinical value of these amino acids. The final chapter provides an extensive and up-to-date listing of relevant websites and other resources. The first four chapters discuss the importance of these amino acids in patients who are losing muscle mass and may at the same time show symptoms of insulin resistance. Chapter 17 provides an overview of the most promising therapeutic uses of branched chain amino acids. Topics discussed include the effects of physical immobility in the elderly, cancer cachexia, and weight reduction in the obese patient. The common thread is the loss of muscle mass and the potential for leucine and/or branched chain amino acid-rich protein supplementation to reduce the muscle loss seen in these conditions. Chapter 18 reviews the data that link liver cirrhosis with insulin resistance. Insulin resistance increases in chronic liver disease and is a risk factor for the progression of liver disease, the potential for the development of liver cancer, and a decrease in long-term survival. The authors suggest that insulin resistance should be considered as an important therapeutic target in patients at any stage of chronic liver disease. They hypothesize that branched chain amino acids play a dual role in glucose metabolism in skeletal muscle, enhancing glucose uptake under normal insulin conditions while causing insulin resistance under high insulin conditions. The next chapter concentrates on the actions of leucine on glucose metabolism. Since its discovery, leucine has been shown to affect glucose homeostasis in liver, muscle, adipose tissue, and pancreatic β cells. In the β cells, leucine acutely stimulates insulin secretion by several mechanisms. These mechanisms can be modulated by factors that include, but are not limited to, the body weight of the patient, whether they are type 2 diabetics and whether or not they routinely exercise. Chapter 20 focuses on protein metabolism during insulin resistance and the effects of surgically implemented weight loss on branched chain amino acid status and requirements. Elevated plasma amino acid levels have been associated with obesity and insulin resistance and circulating branched chain amino acids have been identified as early biomarker predictors of diabetes risk in obese insulin-resistant subjects. The chapter includes detailed discussions of the results of bariatric surgery on branched chain amino acid levels and examines the data from twin studies to better understand the interactions between branched chain amino acid status and improvements in glucose control following acute, significant weight loss.

Chapter 21 examines the metabolism of branched chain amino acids within the skin and provides a unique perspective on the importance of these amino acids, especially leucine, in stimulating dermal collagen synthesis in wound healing. The chapter reviews the requirements for mixtures of amino acids to optimize skin collagen formation in the face of protein malnutrition, wound healing, and UV radiation and discusses the mechanism of action of these stressor to the skin. Chapter 22 reviews the potential for branched chain amino acid supplementation to reduce the muscle wasting seen in boys that have inherited the genetic disorder, Duchenne muscular dystrophy (DMD). The disease is characterized by progressive loss of muscle mass and accumulation of body fat. Steroids (e.g., prednisone) are the only treatment available at this time, but the drugs increase the accumulation of body fat and have other adverse side effects. The chapter provides a strong biochemically based rationale for

supplementing DMD patients with branched chain amino acids; however as yet, there are no large, well-controlled and patient-monitored intervention studies.

Part III, above, contained chapters that consistently reported a decreased branched chain amino acid status in patients with liver diseases including liver cancer. The next two chapters investigate branched chain amino acid supplementation in patients with serious liver diseases. Chapter 23 examines the potential for branched chain amino acid supplementation to reduce the adverse effects of radiotherapy used in patients with liver cancer. The chapter reviews the recent development of radiotherapeutic technologies that permit their application in this patient population. The authors inform us that most of the patients undergoing radiation therapy have chronic liver disease and frequently also have protein-calorie malnutrition. In addition, radiation can result in general fatigue, nausea, and vomiting that further aggravate the patients' nutritional status. Preliminary clinical investigations suggest that supplementation with branched chain amino acids during radiation therapy helped to reduce the loss of these amino acids and may be of benefit in maintaining albumin levels. Chapter 24 describes the condition called hepatic encephalopathy, which is a metabolic neuropsychiatric syndrome of cerebral dysfunctions due to severe chronic or acute liver disease. The manifestations of hepatic encephalopathy range from minor symptoms with personality changes and altered sleep patterns to deep coma. The chapter includes a detailed review of all clinical trials and meta-analyses that included studies where patients have been given branched chain amino acids for the treatment of hepatic encephalopathy regardless of route of administration. The combined evidence supported the use of oral branched chain amino acids as treatment for patients with hepatic encephalopathy based upon the results from several large, high-quality randomized controlled trials. However, further research is required to determine the optimal dose of these amino acids.

The above descriptions of the two volumes' 46 chapters attest to the depth of information provided by the 156 well-recognized and respected editors and chapter authors. Each chapter includes complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. Key features of the two comprehensive volumes include over 250 detailed tables and informative figures, an extensive, detailed index, and more than 1,900 up-to-date references that provide the reader with excellent sources of worthwhile information. Moreover, the final chapter contains a comprehensive list of web-based resources that will be of great value to the health provider as well as graduate and medical students.

In conclusion, *Branched Chain Amino Acids in Clinical Nutrition*, a two-volume book, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of branched chain amino acids in maintaining the nutritional status and overall health of the individual especially in certain disease conditions. The volumes will serve the reader as the benchmarks in this complex area of interrelationships between dietary protein intakes and individual amino acid supplementation, the unique role of the branched chain amino acids in the synthesis of brain neurotransmitters, collagen formation, insulin and glucose modulation, and the functioning of all organ systems that are involved in the maintenance of the body's metabolic integrity. Moreover, the physiological, genetic, and pathological interactions between plasma levels of branched chain amino acids and aromatic amino acids are clearly delineated so that students as well as practitioners can better understand the complexities of these interactions. Unique chapters examine the effects of branched chain amino acid status and the effects of genetic mutations from pre-pregnancy, during fetal development and birth, and infancy through the aging process. The editors are applauded for their efforts to develop the most authoritative and unique resource in the area of branched chain amino acids in health and disease to date and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N.
Series Editor

About the Series Editor

Adrianne Bendich, Ph.D., F.A.S.N., F.A.C.N. has served as the "Nutrition and Health" Series Editor for over 15 years and has provided leadership and guidance to more than 120 volume editors that have developed the 60+ well-respected and highly recommended volumes in the series.

In addition to ***Branched Chain Amino Acids in Clinical Nutrition*** **volume I and volume II, edited by Rajkumar Rajendram M.D., Victor R. Preedy Ph.D., and Vinood B. Patel Ph.D**., **major new editions** in 2012–2014 include:

1. ***Glutamine in Clinical Nutrition,*** edited by Rajkumar Rajendram M.D., Victor R. Preedy Ph.D., and Vinood B. Patel Ph.D., 2014
2. ***Handbook of Clinical Nutrition and Aging, Third Edition,*** edited by Connie W. Bales Ph.D., RD, Julie L. Locher Ph.D., MSPH, and Edward Saltzman, M.D., 2014
3. ***Nutrition and Oral Medicine, Second Edition,*** edited by Dr. Riva Touger-Decker, Dr. Connie C. Mobley, and Dr. Joel B. Epstein, 2014
4. ***Fructose, High Fructose Corn Syrup, Sucrose and Health,*** edited by Dr. James M. Rippe, 2014
5. ***Nutrition in Kidney Disease, Second Edition,*** edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2014
6. ***Handbook of Food Fortification and Health, volume I*** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
7. ***Handbook of Food Fortification and Health, volume II*** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
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Dr. Bendich is President of Consultants in Consumer Healthcare LLC, and is the editor of ten books including ***Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fourth Edition*** co-edited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the *Journal of Nutrition in Gerontology and Geriatrics*, and *Antioxidants*, and has served as Associate Editor for *Nutrition* the International Journal; served on the Editorial Board of the *Journal of Women's Health and Gender-Based Medicine*, and served on the Board of Directors of the American College of Nutrition.

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI)

intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. She is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* Awardee, and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences. Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN. Dr. Bendich is an Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.

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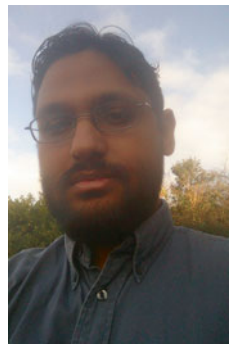

Dr. Rajkumar Rajendram is an intensivist, anesthetist, and perioperative physician. He graduated in 2001 with a distinction from Guy's, King's, and St. Thomas Medical School, in London. As an undergraduate he was awarded several prizes, merits, and distinctions in preclinical and clinical subjects. This was followed by training in general medicine and intensive care in Oxford, during which period he attained membership of the Royal College of Physicians (MRCP) in 2004. Dr. Rajendram went on to train in anesthesia and intensive care in the Central School of Anaesthesia, London Deanery and became a fellow of the Royal College of Anaesthetists (FRCA) in 2009. He has completed advanced training in intensive care in Oxford and was one of the first intensivists to become a fellow of the faculty of intensive care medicine (FFICM) by examination. He coauthored the Oxford Case Histories in Cardiology which was published by the Oxford University Press in 2011. He is currently preparing the text for the Oxford Case Histories in Intensive Care. His unique training and experience has been tailored for a career in intensive care with a subspecialty interest in perioperative medicine.

Dr. Rajendram recognizes that nutritional support is a fundamental aspect of critical care. He has therefore devoted significant time and effort into nutritional science research. As a visiting research fellow in the Nutritional Sciences Research Division of King's College London he has published over 50 textbook chapters, review articles, peer-reviewed papers, and abstracts from his work.

Victor R. Preedy B.Sc., Ph.D., D.Sc., FSB, FRSH, FRIPHH, FRSPH, FRCPath, FRSC, is a senior member of King's College London (Professor of Nutritional Biochemistry) and King's College Hospital (Professor of Clinical Biochemistry; Hon). He is attached to both the Diabetes and Nutritional Sciences Division and the Department of Nutrition and Dietetics. He is also Director of the Genomics Centre and a member of the School of Medicine. Professor Preedy graduated in 1974 with an Honors Degree in Biology and Physiology with Pharmacology. He gained his University of London Ph.D. in 1981. In 1992, he received his Membership of the Royal College of Pathologists and in 1993 he gained his second doctoral degree, for his contribution to the science of protein metabolism in health and disease. Professor Preedy was elected as a Fellow of the Institute of Biology in 1995 and to the Royal College of Pathologists in 2000. Since then he has been elected as a Fellow to the Royal Society for the Promotion of Health (2004) and the Royal Institute of Public Health and Hygiene (2004). In 2009, Professor Preedy became a Fellow of the Royal Society for Public Health and in 2012 a Fellow of the Royal Society of Chemistry. In his career Professor Preedy worked at the National Heart Hospital (part of Imperial College London) and the MRC Centre at Northwick Park Hospital. He has collaborated with research groups in Finland, Japan, Australia, the USA, and Germany. He is a leading expert on biomedical sciences and has a longstanding interest in how nutrition and diet affects well-being and health. He has lectured nationally and internationally. To his credit, Professor Preedy has published over 500 articles, which include peer-reviewed manuscripts based on original research, reviews, and numerous books and volumes.

Dr. Vinood B. Patel is currently a Senior Lecturer in Clinical Biochemistry at the University of Westminster and honorary fellow at King's College London. He presently directs studies on metabolic pathways involved in liver disease, particularly related to mitochondrial energy regulation and cell death. In addition, research is being undertaken to study the role of nutrients, phytochemicals, and fatty acids in the development of fatty liver disease and iron homeostatic regulation. Another area includes identifying new biomarkers that can be used for diagnosis and prognosis of liver disease. Dr. Patel graduated from the University of Portsmouth with a degree in Pharmacology and completed his Ph.D. in protein metabolism from King's College London in 1997. His postdoctoral work was carried out at Wake Forest University Baptist Medical School studying structural–functional alterations to mitochondrial ribosomes, where he developed novel techniques for characterizing their biophysical properties. Dr. Patel is a nationally and internationally recognized alcohol researcher and was involved in several NIH-funded biomedical grants related to alcoholic liver disease. Dr. Patel has edited biomedical books in the area of nutrition and health prevention, autism, and biomarkers and has published over 160 articles.

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