

Symposium: Dairy Product Components and Weight Regulation

The Role of Leucine in Weight Loss Diets and Glucose Homeostasis^{1,2}

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ABSTRACT Debate about the optimum balance of macronutrients for adult weight maintenance or weight loss continues to expand. Often this debate centers on the relative merits or risks of carbohydrates vs. fats; however, there is increasing interest in the optimal level of dietary protein for weight loss. Diets with a reduced ratio of carbohydrates/protein are reported to be beneficial for weight loss, although diet studies appear to lack a fundamental hypothesis to support higher protein intakes. Presently, needs for dietary proteins are established by the recommended daily allowance (RDA) as the minimum level of protein necessary to maintain nitrogen balance. The RDA define the primary use of amino acids as substrates for synthesis of body proteins. There is emerging evidence that additional metabolic roles for some amino acids require plasma and intracellular levels above minimum needs for protein synthesis. The branched-chain amino acid leucine is an example of an amino acid with numerous metabolic roles that function in proportion with cellular concentration. This review provides an overview of the current understanding of metabolic roles of leucine and proposes a metabolic framework to evaluate the merits of a higher protein diet for weight loss. *J. Nutr.* 133: 261S–267S, 2003.

KEY WORDS: • obesity • weight management • diabetes • protein • leucine • insulin

Obesity is a major public health concern in the United States (1). Management or prevention of chronic adult weight gain is becoming a primary focus of adult health care. Approaches for control of adult body weight are diverse, but all approaches ultimately return to the fundamental concept of energy balance. To maintain body weight, dietary intake of energy must be balanced with daily expenditure of energy.

Although energy intake is a straightforward concept, the ideal balance of macronutrients for adult health and maintenance of ideal body weight remains controversial. Presently, most nutrition recommendations focus on lowering the lipid content of the diet. Concerns about energy density and the associations of blood cholesterol and saturated fatty acids (SFA)⁴ with coronary heart disease lead nutrition recommendations to focus on reducing dietary fat and particularly animal

fats (2,3). Current recommendations target a minimum level of dietary fat of ~60 g/d or less.

Similar logic has been applied to dietary protein. Current recommended daily allowance (RDA) guidelines are set at minimum levels necessary to prevent deficiency. Nearly all Americans consume protein at levels above the RDA (4). Further, because protein foods are typically more expensive and often associated with saturated fat, recommendations target a minimum level of dietary protein of ~70 g/d. Together the recommendations for fat and protein provide a total energy intake of 820 kcal/d. Estimates for average daily energy consumption in the United States are ~2100 kcal/d (4). So, by default, current nutrition policy recommends that Americans consume at least 320 g/d (1280 kcal) of carbohydrates with a ratio of carbohydrate/protein >3.5. Nutrition surveys (4) indicate that the public response to these recommendations is that during the past three decades, Americans increased consumption of high glycemic carbohydrates in the forms of refined carbohydrates from breads, cereals and pasta and of sugars from soda and fruit drinks.

What is the dietary need for carbohydrate and are there any risks associated with high carbohydrate intakes? Currently, there is not a minimum RDA established for carbohydrates. However, tissues that are obligate users of glucose for energy set a minimum threshold for metabolic needs for carbohydrates. These tissues, including the brain, nervous tissues and blood cells, use ~100 to 120 g of glucose/d (5,6). Comparing the minimum metabolic needs for carbohydrate and protein suggests a dietary ratio of carbohydrate/protein (100 g/70 g) of ~1.5. Thus, current nutrition practice recommends a balance

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⁴ Abbreviations used: BCAA, branched-chain amino acid; DRI, Dietary Reference Intakes; GNG, gluconeogenesis; RDA, recommended daily allowance; SFA, saturated fatty acid; UL, upper limit.

of macronutrients with minimum levels of dietary protein and fat and maximum intakes of carbohydrates. On the other hand, there is increasing evidence that high carbohydrate diets reduce oxidation of body fat (7,8), increase blood triglycerides (9–11) and reduce satiety (12). These reports raise new questions about the ideal ratios of macronutrients to balance energy needs for adults.

In 1994 the Food and Nutrition Board of the National Academy of Science began to emphasize that for any nutrient there is a range of dietary intakes to support optimal metabolic needs. This concept of an optimal range is reflected in the Dietary Reference Intakes (DRI) (13). The DRI (Fig. 1) recognize that metabolic needs range from a minimum level necessary to prevent deficiencies (the current RDA) to an upper limit (UL) where higher intakes may produce adverse effects of excess or toxicity. For vitamins and minerals, the DRI concept of range is readily accepted; however, for the macronutrients the concept of optimal metabolic range remains relatively untested.

Application of the DRI concept of range of intake to the macronutrients is complicated by the diversity of their functions. For protein, the RDA (Fig. 1) is defined as the minimum protein needed to maintain short-term nitrogen balance under conditions of controlled energy intake. Nitrogen balance is a concept that is particularly useful for a limiting amino acid such as lysine that serves as an essential amino acid for peptide structures and has limited use as a metabolic substrate (14,15). At the other end of the spectrum, leucine, one of the branched-chain amino acids (BCAA), is an essential amino acid with a role similar to that of lysine for protein synthesis, although leucine also participates in critical metabolic processes (16,17). These differences in roles among amino acids suggest that a single definition of minimum requirements may not be adequate to encompass the full range of human needs for each of the nine indispensable amino acids.

The three BCAA, leucine, valine and isoleucine, support numerous metabolic processes ranging from the fundamental role as substrates for protein synthesis to metabolic roles as energy substrates (18), precursors for synthesis of alanine and glutamine (19,20) and as a modulator of muscle protein synthesis via the insulin-signaling pathway (21–23). The potential for the BCAA to participate in each of these metabolic processes appears to be in proportion to their availability. Experimental evidence comparing the priority for use of the BCAA for each of these individual processes is limited, but suggests that the first priority is for synthesis of protein structures (24). By use of leucine as an example, daily needs for new proteins on the basis of nitrogen balance are estimated at 1 to 4 g/d (25). When the minimum need for protein synthesis is met, leucine is available to contribute to production of alanine

TABLE 1

Leucine and BCAA content of foods¹

Food	Leucine	BCAA
	%	
Whey protein isolate	14	26
Milk protein	10	21
Muscle protein	8	18
Soy protein isolate	8	18
Wheat protein	7	15

¹ Values reflect grams of amino acids/100 g of protein. Source: USDA Food Composition Tables.

and glutamine or to impact the signaling pathway. These roles are dependent on increasing intracellular concentrations (18,19,26). Metabolic use of leucine is estimated at 7 to 12 g/d (27,28). These data support the hypothesis that the potential impact of the BCAA on metabolic processes is proportional to their dietary intake.

Leucine, valine and isoleucine are relatively abundant in the food supply, accounting for 15 to 25% of the total protein intake, with dairy products being particularly rich sources of the BCAA (Table 1). Considering their relative abundance, it is somewhat surprising that the BCAA are the only amino acids not degraded in the liver. For the other 17 amino acids, the liver and gut function as regulatory organs to manage the rate of appearance of dietary amino acids into blood circulation. However, for the BCAA, dietary intake directly impacts plasma levels and concentrations in peripheral tissues including skeletal muscle and adipose.

Associated with increased cell concentration of the BCAA, there is increased catabolism of the BCAA in peripheral tissues. Degradation of the BCAA in skeletal muscle is linked to production of alanine and glutamine and maintenance of glucose homeostasis. The interrelationship between BCAA and glucose metabolism was first reported associated with the glucose-alanine cycle (19,20). As a part of this cycle, there is a continuous release of BCAA from the liver and splanchnic bed with movement of the BCAA through the blood to skeletal muscle (Fig. 2). Uptake by muscle tissue increases intracellular concentration and stimulates transamination of the BCAA involving transfer of the amino nitrogen from the BCAA to pyruvate producing alanine. Alanine is released

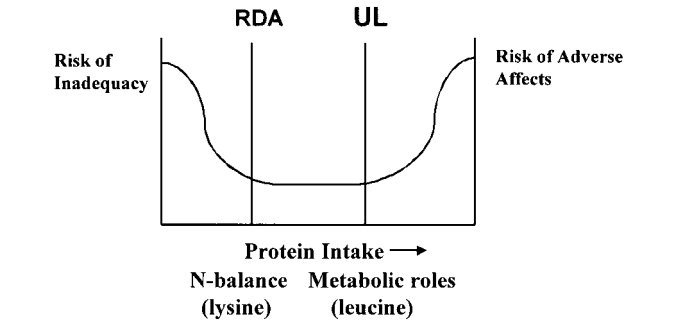


FIGURE 1 Dietary Reference Intakes [modified from Food and Nutrition Board, 1994 (13)]. UL, upper limit.

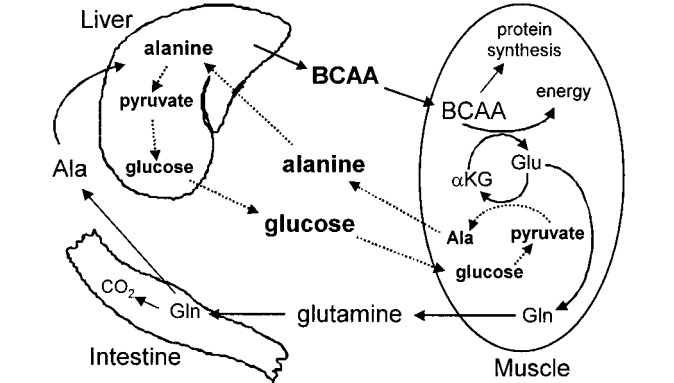


FIGURE 2 Interorgan movement of branched-chain amino acids (BCAA). Ala, alanine; Gln, glutamine; Glu, glutamate; αKG, alpha-keto-glutarate.

from muscle, circulates through blood and is extracted by the liver to support hepatic gluconeogenesis (GNG). Although the significance of the glucose-alanine cycle has been debated, Ahlborg et al. (19) reported that the glucose-alanine cycle accounted for >40% of endogenous glucose production during prolonged exercise.

More recently, the overall contribution of dietary amino acids to glucose homeostasis received further support on the basis of quantitative evaluations of hepatic glucose production. Jungas et al. (29) provided an elegant argument that amino acids serve as a primary fuel for the liver and the primary carbon source for hepatic GNG. Other investigators (30,31) extended this thinking with the findings that endogenous glucose production in the liver is a critical factor in maintenance of blood glucose. After an overnight fast, GNG provides >70% of hepatic glucose release, with amino acids serving as the principal carbon source (31). These studies provide further evidence for a linkage between dietary protein and glucose homeostasis.

In addition to the relationship of BCAA to glucose homeostasis, increased concentrations of leucine have the potential to stimulate muscle protein synthesis during catabolic conditions associated with food restriction (32–34) or after exhaustive exercise (35,36). Providing leucine orally either alone (35,37) or as part of a complete meal (36,38) increases plasma and intracellular levels of leucine. The increase in leucine concentration is sensed by an element of the insulin-signaling pathway and triggers a phosphorylation cascade that stimulates the translational initiation factors eIF4 and p70^{S6}K (Fig. 3). These initiation factors are critical for stimulation of muscle protein synthesis (39) and suggest that dietary levels of leucine may influence maintenance of muscle mass during weight loss.

These findings establish the potential for dietary levels of the BCAA, leucine, valine and isoleucine, to influence both glucose homeostasis and protein turnover, particularly during a hypocaloric period such as weight loss. Current dietary practices recommend a diet based on a minimum intake of protein (the RDA) (40) with a maximum intake of carbohydrates (UL). However, applying the DRI concept to the macronutrients allows for the potential to reverse the roles targeting a low level of carbohydrates with the UL-level of protein. In the first case, a high carbohydrate diet would require insulin to manage acute changes in blood glucose associated with high carbohydrate meals and would minimize the role of amino acids in metabolism beyond the basic role as substrates for protein synthesis. In the second case, a diet with low carbohydrates

and increased protein would reduce the role of insulin in managing acute changes in blood glucose and maximize the liver's role in regulating blood glucose through hepatic GNG. Although this metabolic balance is oversimplified here, the concept has been used for management of type 2 diabetes for many years (41). Using the DRI concept of a "healthy range" of nutrient intake provides a framework and a testable hypothesis to evaluate the impact of changes in the dietary ratio of carbohydrate/protein on weight loss, changes in body composition and glucose homeostasis.

To evaluate this hypothesis, we conducted a pair of human weight loss trials by comparing weight loss and metabolic responses between subjects consuming diets with ratios of carbohydrate/protein of 3.5 vs. 1.5 and with protein intakes of 0.8 or 1.5 g/kg · d (42–45). For both studies, subjects in each group received diets that were isocaloric (~1700 kcal/d) and equal in daily intake of fat (~50 g/d) and fiber (~20 g/d). The energy level was selected to produce an energy deficit of at least 500 kcal/d and a weight loss of at least 1 pound/wk. The control diet (Carbohydrate Group) was based on current dietary guidelines for dietary fat at 30% of energy intake and the RDA for protein of 0.8 g/kg · d. Through use of these parameters, a weight loss diet with ~1700 kcal/d provides ~240 g of carbohydrates, 70 g of protein (carbohydrate/protein ~ 3.5) and 50 g of fat with daily leucine intake of ~5 g (Leu at 8% of dietary protein). The second diet treatment (Protein Group) was designed to provide 10 g/d of leucine (protein = 1.5 g/kg · d) with a 1/1 exchange of protein for carbohydrates, producing a carbohydrate/protein ~ 1.5. Subjects in both studies were adult women ranging in age from 40 to 56 y with average body mass index of 31. Exercise was constant within each study. Subjects in Study 1 maintained normal daily activities with no defined exercise, whereas subjects in Study 2 had a defined exercise program 5 d/wk, producing an additional energy expenditure of ~ 300 kcal/d. Study 1 lasted for 10 wk and Study 2 lasted for 16 wk.

Changes in body weight and body composition for the two studies are presented in Tables 2–4. After consuming the respective diets for 10 wk, weight loss was similar for subjects in both groups (Table 2). In both studies, subjects in the Protein Group tended to lose more weight, although the difference was not statistically significant at 10 wk. In Study 2 after 16 wk with the combined effects of diet plus exercise, subjects in the Protein Group lost significantly more weight than did subjects in the Carbohydrate Group.

The composition of the weight loss is presented in Tables 3 and 4. The Protein Group consistently lost more body fat and less lean body mass than did the Carbohydrate Group. In Study 1 after 10 wk, the individual differences in body fat and lean body mass were not statistically different; however, expressing the composition changes as the ratio of fat/lean loss emphasizes the differences between the treatments (Fig. 4). In Study 2, after 16 wk of weight loss, the differences between treatments in changes in body fat and lean tissue were both statistically significant. In total, these data suggest that a diet with increased protein and reduced carbohydrates partitions weight loss toward body fat while sparing body protein. These findings are consistent with other studies that used diets with reduced ratios of carbohydrate/protein (16,46,47).

Although the differences between the treatments appear consistent with other published research, the reasons for the increased weight loss and fat loss remain unclear. Lower food intake or higher levels of physical activity could account for the increased weight loss in the Protein Group. In our studies, both of these factors were controlled and seem unlikely; however, quantitative measures of food intake or physical activity

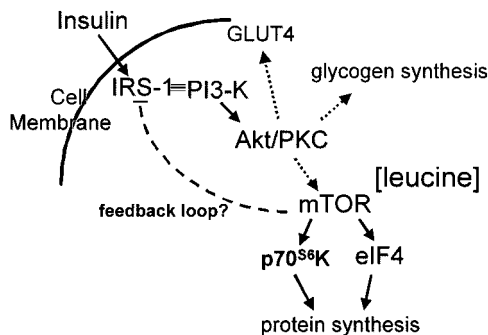


FIGURE 3 Insulin signaling cascade [adapted from Layman (17) and Anthony et al. (39)]. IRS-1, insulin receptor substrate 1; PI3-K, phosphatidylinositol-3 kinase; GLUT4, insulin-dependent glucose transporter; PKC, protein kinase C; mTOR, mammalian target of rapamycin; eIF4, translational initiation factor 4.

TABLE 2

Body weight loss¹

Group	4 wk	10 wk	16 wk
Protein group			
Study 1	8.5	16.6	
Study 2	8.2	15.8	21.6
Carbohydrate group			
Study 1	7.1	15.3	
Study 2	7.1	12.7	14.8*

¹ Weight in pounds; pooled SEM \pm 3.5.* Treatments were statistically different, $P < 0.05$.

always retain uncertainty. Other potential explanations for the differences in body weight and body composition include the following: 1) lower energy efficiency with the higher protein diet (46,48,49); 2) lower insulin response with the reduced carbohydrate diet (50–52); or 3) protein-sparing effect of protein or leucine on lean body mass (17,53). Review of the literature provides support for each of these mechanisms, suggesting that any or all may contribute to the weight and composition changes.

To further evaluate the impact of changes in the dietary ratio of carbohydrate/protein, we examined changes in blood levels of glucose, insulin and amino acids under fasting and postprandial conditions. Frequently, studies of the interactions of insulin, glucose and amino acids are done as acute experiments, with minimal concern for energy status. For example, a common technique used to study acute glucose or insulin regulation is the euglycemic, hyperinsulinemic clamp. In this case, the baseline or control condition consists of steady-state infusion of insulin and glucose at levels above normal physiological values. Then the experimental treatment is added on top of this baseline condition. Hence, when amino acids are infused on top of the euglycemic clamp in amounts that increase blood amino acid concentrations by two- to fourfold, the results demonstrate that amino acids increase insulin levels and reduce glucose uptake into muscle (49,50). On the other hand, if proteins (i.e., amino acids) are substituted into a diet in place of an equal amount of carbohydrate, the higher protein diet reduces the acute insulin response to a meal (49). Our studies used the isocaloric diet model with a direct gram-for-gram substitution of protein for carbohydrates. Under conditions of controlled food intake, we examined changes in plasma amino acids, glucose and insulin during fasting and postprandial periods.

After a 12-h overnight fast, plasma levels of the indispensable amino acids, leucine and threonine, were similar in sub-

TABLE 3

Body fat loss¹

Group	4 wk	10 wk	16 wk
Protein group			
Study 1	6.9	12.5	
Study 2	8.6	15.3	19.4
Carbohydrate group			
Study 1	5.7	10.4	
Study 2	5.5	10.9*	12.3*

¹ Weight in pounds; pooled SEM \pm 2.7.* Treatments were statistically different, $P < 0.05$.

TABLE 4

Lean body mass changes¹

Group	4 wk	10 wk	16 wk
Protein group:			
Study 1	−1.2	−1.9	
Study 2	+1.1	+0.4	−0.9
Carbohydrate group			
Study 1	−1.3	−2.7	
Study 2	−1.1*	−1.8*	−2.4*

¹ Weight in pounds; pooled SEM \pm 0.6.* Treatments were statistically different, $P < 0.05$.

jects consuming either the protein or carbohydrate diets (Table 5). However, the concentrations of the dispensable amino acids alanine and glutamine were both increased. The increases in plasma levels of alanine and glutamine for subjects in the Carbohydrate Group is surprising, given that they consumed equal energy intake and 50% less protein than did the Protein Group. Possible sources of the alanine and glutamine could be increased protein breakdown or increased de novo synthesis in skeletal muscle. Although the Carbohydrate Group appears to lose more lean body mass, it is unlikely that this loss could be detected as a change in short-term protein turnover or as plasma amino acid concentrations. Further, an increase in protein breakdown that altered the plasma concentration of alanine should also increase plasma concentrations of the essential amino acids leucine and threonine.

A second possible explanation for the increase in alanine and glutamine could be de novo synthesis. However, the source of the amino nitrogen for de novo synthesis is leucine or the other BCAA. Increased synthesis of alanine and glutamine requires increased degradation of the BCAA and should be associated with a corresponding decrease in leucine (18).

A third and most likely explanation for the increase in alanine and glutamine would be a decrease in utilization or clearance. Uptake of alanine by the liver is dependent on plasma alanine concentration and the rate of alanine use for hepatic GNG (54,55). Under conditions of high carbohydrate feeding, rates of GNG are downregulated (31) and under conditions of chronic feeding there is transcriptional down-

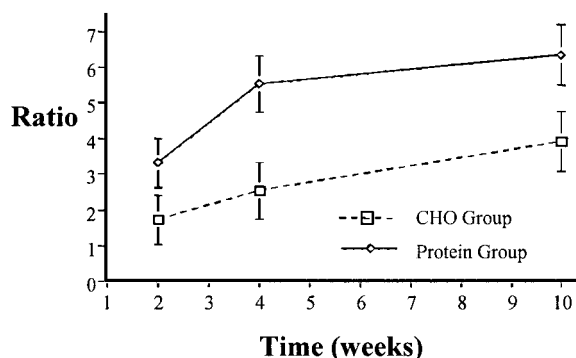


FIGURE 4 Time course of changes in body composition are presented as the ratio of loss of body fat compared with loss of mineral-free lean body mass determined by DXA measurements. Values represent means \pm SEM, $n = 12$. Values with * indicate treatments are statistically different at $P < 0.05$.

TABLE 5

Plasma values after 10 wk on diets^{1,2}

Plasma value	Protein group	Carbohydrate group
12-h fasted values		
Leucine	101.9 ± 4.6 ^a	99.0 ± 4.1 ^a
Threonine	104.5 ± 7.2 ^a	106.5 ± 11.9 ^a
Alanine	324.0 ± 16.3 ^a	388.0 ± 20.6 ^b
Glutamine	378.0 ± 15.2 ^a	449.0 ± 12.0 ^b
Glucose	4.89 ± 0.11 ^a	4.33 ± 0.10 ^b
Insulin	176 ± 18	178 ± 18
2-h postprandial values ³		
Leucine	180.7 ± 9.1 ^b	93.0 ± 4.0 ^a
Threonine	127.1 ± 10.9 ^b	113.1 ± 11.3 ^{a,b}
Alanine	485.0 ± 28.2 ^c	452.0 ± 24.7 ^c
Glutamine	513.0 ± 24.2 ^b	363.0 ± 19.1 ^a
Glucose	4.34 ± 0.15 ^b	3.77 ± 0.14 ^c
Insulin	251 ± 21	384 ± 27

¹ Values represent means ± SEM, $n = 12$ with units as amino acids ($\mu\text{mol/L}$), glucose (mmol/L) and insulin (pmol/L).

² Table adapted from Layman et al. (44).

³ Postprandial values are determined 2 h after consumption of a 400-kcal breakfast meal reflecting the macronutrient content of the respective diets (see text).

regulation of the pathway at key enzymes (52). These data suggest that consumption of a high carbohydrate diet reduces endogenous capacity for glucose production and use of alanine as a GNG substrate. Our study supports this relationship. Subjects consuming the high carbohydrate diet maintained statistically lower blood glucose and higher levels of alanine after 10 wk on the diets (Table 5) and the lower level of fasting blood glucose represents a time-course change associated with the prolonged feeding regimen (Fig. 5).

A similar evaluation of glucose homeostasis can be made at the end of a postprandial absorptive period. At the end of the postprandial period when absorption of exogenous glucose is completed, the body must rebalance hepatic glucose release and peripheral clearance to protect blood glucose levels from hypoglycemic responses. The challenge of the postprandial transition is that plasma insulin levels have not yet returned to fasting levels and blood glucose tends to fall below fasting values (56,57). This transition period must be buffered by hepatic release of glucose derived from a combination of glycogen breakdown and GNG. Measurements of the relative contribution of GNG to hepatic glucose production range from 40% (30) to 75% (31). These data suggest that chronic consumption of a high carbohydrate diet producing downregulation of GNG would be likely to accentuate a postprandial hypoglycemia.

To test this hypothesis, we fed each group of subjects a 400-kcal breakfast meal reflective of their specific diet and measured changes in blood amino acids, glucose and insulin 2 h after completion of the meal (44). As expected, subjects in the Protein Group consuming the higher protein meal (33 g of protein and 39 g carbohydrate) exhibited increases in plasma levels of both essential (Leu and Thr) and nonessential (Ala and Gln) amino acids. Subjects in the Carbohydrate Group receiving a low protein meal (10 g of protein and 57 g carbohydrate) exhibited no change in plasma levels of Leu or Thr, a 16% increase in alanine and a 19% decrease in glutamine.

Threonine is a useful marker for amino acid absorption. During absorption, Thr is extensively degraded in the gut and liver, with only about 40% of the meal content reaching the

blood (48). In our study, we found a postprandial increase in plasma Thr of 21% in the Protein Group and 6% in the Carbohydrate Group, reflecting relative protein intakes. On the other hand, the BCAA concentrations (illustrated by Leu) measured at 2 h after the meal were increased by over 80% in the Protein Group but actually declined by 6% in the Carbohydrate Group. Unlike threonine, the BCAA are not extensively metabolized in the splanchnic bed and largely appear in the blood after a meal (48). Their concentration is regulated by the disposable rate in peripheral tissues (18). In skeletal muscle, degradation of BCAA is directly related to the production of alanine and glutamine that serve as amino-nitrogen carriers (Fig. 2). For subjects in the Protein Group, increased BCAA produced an increase in plasma levels of alanine plus glutamine of 300 $\mu\text{mol/L}$, whereas the Carbohydrate Group had a decrease in plasma BCAA of 6% and a parallel decrease in alanine plus glutamine of 22 $\mu\text{mol/L}$. These changes in plasma amino acid concentrations suggest different potentials for the glucose-alanine cycle to provide substrate for hepatic GNG.

Glucose and insulin status was different between the two treatments. For both diet groups, 2-h postprandial blood glucose values were below fasting levels (Table 5). This decline in blood glucose is associated with the end of absorption of exogenous glucose and the transition to endogenous glucose production. However, values for the Carbohydrate Group were >30% below their fasting level and >30% less than postprandial values for the Protein Group. Associated with the plasma glucose values, both groups maintained blood insulin at levels above fasting values (Table 5). Subjects in the Carbohydrate Group had insulin values that were more than double fasting levels and >40% above those of the Protein Group. These findings are consistent with previous reports (52,56,57) that high carbohydrate diets increase acute insulin response to a meal and inhibit GNG. Further, these data indicate that changes in the ratio of dietary carbohydrate/protein designed to limit dietary carbohydrates and increase protein and BCAA intake serve to stabilize fasting and postprandial blood glucose during food restriction for weight loss.

Driven by emerging literature about dietary carbohydrates and metabolic roles of the BCAA, there is increasing need to reevaluate the balance of carbohydrate/protein in diets for adults. The new DRI values appear to provide a framework to examine macronutrient needs across a range of safe and adequate intakes. For protein the low end of this range has been extensively tested and is generally accepted as the current

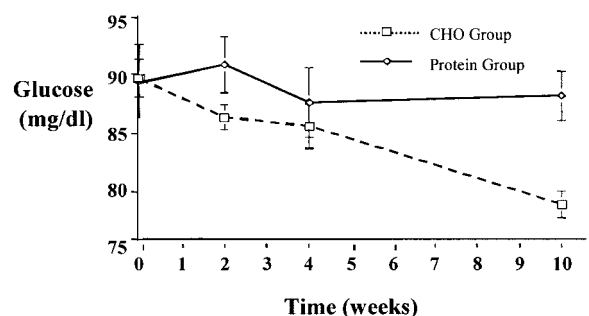


FIGURE 5 Average blood glucose values for subjects on weight loss diets measured after a 12-h overnight fast. Subjects in the Protein Group had no change in fasting blood glucose during the 10 wk of hypocaloric feeding, whereas subjects in the Carbohydrate Group exhibit a significant linear decline ($R^2 = 0.982$; $f = 0.0086$) that is statistically different from that of the Protein Group at 10 wk ($P < 0.05$). Values represent means ± SEM, $n = 12$.

RDA of 0.8 g/kg · d. At present, the UL for protein is unknown. Investigators are advocating a range of protein intakes from 0.8 to 2.0 g/kg · d (16,27,44,46,58). However, recommendations for increased protein intakes are often countered by concerns for negative effects on renal function (3,59).

The impact of dietary protein intake on renal function has been debated for 50 y (60). In cases with compromised renal function, reduced levels of dietary protein can retard the progression to renal failure. Conditions such as in diabetes, hypertension, infection or renal surgery often lead to changes in renal physiology, including increases in glomerular capillary pressure and blood flow rates (59). Restriction of dietary protein appears to reduce the "renal workload" and minimize glomerular perfusion. By extrapolation, it is often suggested that adults avoid high protein intakes to minimize glomerular filtration rates. However, there is no known association of protein intake with progressive renal insufficiency during aging (59,61). Further, there appear to be no negative effects on renal function of long-term daily protein intakes ranging from 1.2 to 2.0 g protein/kg body weight (58) and renal clearance is highly efficient at intakes up to 3.0 g/kg · d (62).

In summary, there is increasing evidence that the BCAA, and specifically leucine, have unique roles in metabolic regulation beyond the fundamental role of amino acids as substrates for synthesis of proteins. These roles include a direct link to maintenance of glucose homeostasis by enhancing recycling of glucose via the glucose-alanine cycle and a direct link to translational regulation of muscle protein synthesis through the insulin signaling cascade. The impact of BCAA on these pathways is proportional to availability and dietary intake. We propose that application of these metabolic roles of the BCAA in development of weight management programs will enhance changes in body composition with sparing of lean body mass and will enhance glucose and insulin homeostasis by stabilizing fasting and postprandial levels of blood glucose.

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