

# Long-term effects of leucine supplementation on body composition

Michèle Balage<sup>a,b,c</sup> and Dominique Dardevet<sup>a,b,c</sup>

<sup>a</sup>INRA, UMR 1019 Nutrition Humaine, Saint Genès Champanelle, <sup>b</sup>Clermont Université, UFR Médecine, UMR 1019 Nutrition Humaine and <sup>c</sup>CRNH Auvergne, Clermont-Ferrand, France

Correspondence to Dominique Dardevet, UNH Centre de Clermont-Ferrand-Theix, INRA, 63122 Saint Genès Champanelle, France  
Tel: +33 473 62 45 05; fax: +33 473 62 47 55;  
e-mail: dominique.dardevet@clermont.inra.fr

**Current Opinion in Clinical Nutrition and Metabolic Care** 2010, 13:265–270

## Purpose of review

Leucine does not only serve as a substrate for protein synthesis but is also recognized as a potent signal nutrient that regulates protein metabolism. Accordingly, leucine supplementation has been suggested to develop muscle mass or prevent protein loss in several conditions characterized by muscle protein wasting. In the present review, we reported the recent results related to the effect of dietary leucine or leucine-rich amino acid mixture and proteins on whole body composition.

## Recent findings

Although recent studies corroborate that increasing plasma leucine concentration generally induces an increase in muscle protein synthesis, long-term dietary leucine supplementation has been poorly investigated. Chronic free leucine supplementation alone did not improve lean body or muscle mass during resistance training or in elderly, whereas it was able to limit the weight loss induced by malnutrition. Contradictory data were also reported concerning the effect of leucine supplementation for weight management in obese patients. Leucine-rich amino acid mixture or proteins appeared more efficient than leucine alone to improve muscle mass and performance, suggesting the efficacy of leucine depends nevertheless on the presence of other amino acids.

## Summary

Until now, there is no evidence that chronic leucine supplementation is efficient in promoting muscle mass or preventing protein loss during catabolic states. Further studies are required to determine the duration and nutritional conditions of long-term leucine supplementation and to establish whether such nutritional interventions can help to prevent or treat muscle loss in various pathological or physiological conditions.

## Keywords

body composition, leucine supplementation, muscle mass and strength

Curr Opin Clin Nutr Metab Care 13:265–270  
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1363-1950

## Introduction

In the 1970s, a number of laboratories first demonstrated *in vitro* that among amino acids, branched chain amino acids (BCAAs) and especially leucine have the potential to regulate muscle protein metabolism by stimulating protein synthesis and inhibiting protein degradation [1–3]. Later, it has been clearly confirmed *in vivo* that leucine was also able to stimulate muscle protein synthesis to the same extent as a complete meal [4] and in a dose-dependent manner [5]. The attenuation of *in-vivo* skeletal muscle proteolysis by leucine has been also described but is, however, less documented than for protein synthesis [6]. Leucine serves not only as a substrate for protein synthesis but is also recognized as a potent nutrient signal that regulates protein turnover through activation of cell signaling pathways common to insulin, including the mammalian target of rapamycin complex (mTOR), which, in turn, activates two key regulatory proteins involved in the regulation of trans-

lation initiation such as S6K1 and 4EBP1 [7]. Based on these observations, dietary leucine supplementation has been predicted to represent a useful nutritional tool for increasing muscle mass (in association with exercise) or maintaining muscle protein content in pathological states that induced muscle wasting (cancer, diabetes, exercise, aging). However, despite numerous studies have demonstrated the positive effect of BCAA and/or leucine on muscle anabolism, it is still not obvious that leucine is able to improve muscle mass in long-term supplementation. The purpose of this review is to examine whether long-term dietary leucine or leucine-rich protein supplementation has a beneficial or deleterious effect on body composition in selected physiological situations such as exercise, malnutrition, weight management or aging.

## Leucine supplementation and exercise

Physical activity and exercise training are known to favor muscle mass increase. However, postexercise net protein

balance is positive only with ingestion of amino acids. Despite demonstration by Anthony *et al.* [8] that leucine increased skeletal muscle protein synthesis when given alone in rats following exercise, the efficiency of free leucine supplementation to stimulate muscle protein synthesis in humans after exercise is still controversial. A recent study reported that ingestion of whey hydrolysate, which induced a rapid and large increase in plasma leucine concentration, was more efficient to stimulate muscle protein synthesis after resistance exercise in men than ingestion of soy protein or casein, suggesting that leucine availability might be partly responsible for this beneficial effect [9<sup>\*</sup>]. However, despite a dramatic increase in plasma leucine, co-ingestion of free leucine with whey proteins does not further increase postexercise muscle protein synthesis [10–12,13<sup>\*</sup>]. These studies suggest that leucine may differentially modulate muscle protein metabolism depending on the type of protein ingested and the kinetic of appearance of the other amino acids after exercise.

#### **Chronic leucine supplementation and exercise**

The effect of chronic supplementation with various protein sources has been widely investigated to optimize the effects of exercise on body composition. For example, whey protein is considered as a high-quality protein because it contains large amounts of essential amino acids and is rapidly digested leading to rapid and important leucine availability [14,15]. Young athletes supplemented for 10 weeks with hydrolyzed whey isolate (1.5 g/kg/day), a leucine-rich protein, exhibited a significant increase in lean mass (+7.5%) linked to a significant improvement in strength compared to casein supplementation [16]. An additional 10% reduction in fat mass was even observed in whey isolate-supplemented group. More recently, Hulmi *et al.* [17] also reported that chronic (21 weeks) supplementation with whey proteins favored resistance training-induced muscle hypertrophy in young healthy individuals compared to a nonenergetic placebo. These data suggest that chronic 'high-quality protein' supplementation is able to improve exercise-induced muscle mass gain and performance. However, the role of leucine in those effects is still under question as the effect of long-term leucine supplementation for promoting muscle hypertrophy and/or performance during resistance training remains, surprisingly, poorly documented. To our knowledge, only Crowe *et al.* [18] investigated the effect of 6-week dietary free leucine supplementation (45 mg/kg/day) on body composition and exercise performance on competitive outrigger canoeists. Leucine supplementation did not change whole body mass or percentage of body fat mass compared to placebo supplementation, whereas plasma leucine concentration was significantly increased. Nevertheless, leucine supplementation improved endurance performance by increasing time of exhaustion.

There is some evidence that long-term leucine availability is sufficient to improve muscle mass or performance during exercise training. However, it needs to be associated with other amino acids to be efficient (for example, through leucine-rich proteins).

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#### **Leucine supplementation and maintenance of lean body mass**

Involuntary (malnutrition) or intentionally (nutritional treatment of obesity) weight loss induces reduction in fat mass but is also associated with a reduction in lean body mass. It is, however, necessary to preserve muscle mass because muscle wasting induces a number of dysfunctions that may affect the recovery or health of individuals.

#### **Food restriction and protein malnutrition**

Donato *et al.* [19] studied the effect of a 50% increase in daily leucine intake in adult rats undergoing a 50% food restriction for 6 weeks. The leucine-supplemented rats exhibited significantly greater percentage of lean mass than control rats suggesting that leucine supplementation had preserved lean body mass loss induced by food restriction. Similar results have been observed with intermittent periods of 50% food restriction (1 week) followed by 2-week recovery with *ad libitum* feeding [20]. However, improvement in lean body mass did not translate into increased muscle mass or gastrocnemius protein content in these studies [19,20].

During protein malnutrition in young adult rats (5% casein diet or a protein-free diet for 1 week), leucine supplementation (1.15% of the diet) significantly reduced muscle weight loss [21,22] through inhibition of myofibrillar protein degradation. Conversely, 60-day free leucine supplementation during nutritional recovery after long-term protein deficiency in very young rats (6% casein for 120 days) did not improve whole lean body mass recovery and only tended to improve muscle weight restoration (+7%) [23]. Leucine supplementation seems to be beneficial in reducing lean and muscle mass loss during severe protein malnutrition or food restriction without being fully efficient alone during the recovery period in young growing rats.

#### **Weight management**

The prevalence of obesity had significantly increased during the last decades and is a major public health problem leading to insulin resistance, type II diabetes, hypertension, atherosclerosis and cancers. Many dieting strategies have been proposed to induce short-term weight loss, but long-term weight management is more uncertain. The energy-restricted diets required for weight loss in obesity resulted in the expected body fat loss but also in muscle mass loss. Thus, in order to

prevent muscle loss, the use of high-protein diets or supplementation with BCAA or leucine, based on their anabolic effects, has been suggested [24–27]. Moreover, leucine has been shown to decrease food intake through mTOR activation in the hypothalamus [28] and the stimulation of the leptin secretion, the satiety hormone [29].

In rodents fed a high-fat diet (HFD), leucine supplementation induced a marked reduction in diet-induced weight gain (–20–30%) compared to nonsupplemented diet [30,31\*\*] that resulted from a decrease in body fat without change in lean body mass. This effect has been explained by a decrease in food intake [31\*\*] or an increase in energy expenditure [30]. Increasing leucine intake had prevented the HFD-induced hyperglycemia and improved overall glucose tolerance in mice [30] without effect in rats [31\*\*]. Using a similar diet-induced obesity in mice, Naiziri *et al.* [32\*] reported no beneficial effect of leucine supplementation on body composition, energy expenditure or glucose tolerance.

In humans, chronic moderate-to-high protein diets have been reported to increase weight and fat mass loss with minimizing lean mass loss compared with common reduced-carbohydrate diets in adult obese patients [33,34]. However, to our knowledge, long-term leucine or even BCAA supplementation has not been yet evaluated in any clinical study. Only a study using a whey protein fraction, that is, Prolibra, has shown to enhance weight loss in obese patients, in whom caloric intake was reduced 500 calories per day [35]. After 12 weeks of supplementation, the Prolibra group lost significantly more body fat and less lean muscle mass compared with nonsupplemented participants. However, as Prolibra is enriched in calcium and bioactive peptides, it is not possible to attribute the beneficial effect of such a supplement to unique leucine excess.

The beneficial effect of leucine supplementation alone compared with high-protein diets in weight management or preservation of lean mass in energy-restricted obese patients is not clearly established yet. However, despite the lack of clinical studies, increased leucine availability in obese patients under caloric restriction may be a good nutritional tool to preserve lean and/or muscle mass.

### Leucine supplementation and sarcopenia

Sarcopenia is characterized by a progressive loss of muscle mass and strength, which directly affects the mobility and health of elderly people. The origin of sarcopenia is, of course, multifactorial but may be partly explained by a decreased ability of aged muscle to respond appropriately to anabolic stimuli such as food

intake [36,37]. This defect has been found to result from a decreased response and/or sensitivity of protein synthesis and degradation to physiologic concentrations of amino acids in elderly [38,39]. This was related to a defect of leucine to stimulate S6K1 activity [40] but postprandial stimulation of muscle protein synthesis and inhibition of protein degradation can be restored by a leucine-supplemented meal in either elderly rodent or humans [41–44]. Overall, these data suggested that increasing leucine availability may represent a nutritional strategy to control body composition during aging. However, the long-term effect of leucine via BCAA or leucine-rich protein supplementation has not been extensively investigated.

In rodents, a leucine-supplemented meal given everyday for 10 days was still able to restore the anabolic effect of feeding in old rats [41,42], but the duration of supplementation was not sufficient for muscle mass gain. Until now, long-term leucine supplementation alone in rodents has not been reported. Leucine-rich mixed amino acid mixture (62.5% BCAA, in which leucine constituted 31.3%) given for 1 month in 24-month-old rats has been shown to completely prevent the 30% reduction in total and fractional (myofibrillar, soluble and stromal fractions) muscle protein content observed in old rats [45]. Unfortunately, protein measurements were not associated with any information of muscle weight. Moreover, physical performance of supplemented old rats, determined by measuring the time of exhaustion during a swim test, was also returned to that of young rats (6-months-old). In the study by Pansarasa *et al.* [46] with the same amino acid mixture given for 2 months to 18-month-old rats, cross-sectional area of fibers of the soleus muscle was increased but neither whole body weight or soleus mass was improved after supplementation. No improvement in muscle mass was also observed in old rats fed for 1 month with leucine-rich whey proteins despite an increase in postprandial muscle protein synthesis [15].

Few studies have been undertaken to study the chronic leucine supplementation in elderly humans. Over a 3-month period, a 7.5 g free leucine daily supplementation given in each main meal (2.5 g at breakfast, lunch and dinner) did not induce any increase in total or muscle lean body mass and did not improve muscle strength compared to an isoenergetic placebo [47\*\*]. However, in this study, it is important to note an 18–25% decline in basal plasma valine concentration in the leucine-supplemented group suggesting an amino acid imbalance. Other studies have investigated the effect of long-term supplementation with amino acid mixtures, wherein leucine formed the highest percentage of the mixture (Table 1). It has been reported at first that 3 months of such a supplementation significantly improved muscle strength and physical capacity in healthy elderly people [48–50].

**Table 1** Effect of leucine supplementation on body composition and muscle performance in elderly

Reference	Participants	Source	Supplementation design			Outcomes	
			Corresponding leucine supplement (g/day)	Duration	Body composition	Muscle performance	
Scognamiglio <i>et al.</i> [48]	44 men (> 65 years)	12 g AA mixture (31% leu) vs. placebo	3.73	3 months	nd	↑ ambulatory capacity (+ 18–30%) – ↑ strength (+ 16%)	
Scognamiglio <i>et al.</i> [49]	100 men and women (> 65 years)	12 g AA mixture (31% leu) vs. placebo	3.73	3 months	↔ BMI	↑ ambulatory capacity (+ 26–38%) – ↑ strength (+ 38%)	
Scognamiglio <i>et al.</i> [50]	15 men (> 65 years) with chronic heart failure	2 × 4 g AA mixture (31% leucine) vs. placebo	2.48	3 months	nd	↑ 6-min walk test (+ 12%)	
Solerte <i>et al.</i> [53]	41 healthy men (> 65 years)	2 × 4 g AA mixture (31% leu) vs. placebo	2.48	8–16 months	↑LBM (+13–17%) after 8 months; ↔ fat mass	nd	
Borsheim <i>et al.</i> [51]	12 men and women (67 ± 6 years) with glucose intolerance	2 × 11 g EAA mixture+arg (36% leu) vs. baseline	7.9	4 months	↔ body weight; ↓LBM (+2.4%); ↔ lean leg mass, fat mass; bone mass, fat mass; bone mass	↑leg strength (+ 22%); ↑ physical function (6–12%)	
Dillon <i>et al.</i> [52]	14 healthy women (> 65 years)	2 × 7.5 g EAA mixture (18.6% leu) vs. baseline	2.8	3 months	↔ body weight – ↓LBM (+3.9%) ↔ fat mass	↔ muscle strength	
Verhoeven <i>et al.</i> [47**]	30 healthy men (71 ± 4 years)	3 × 2.5 g leucine vs. placebo	7.5	3 months	↔ LBM, fat, leg lean mass, leg fat	↔ muscle strength	

AA, amino acid; LBM, lean body mass; nd, not determined. ↑ increase, ↔ no change.

Subsequently, it has been shown that 3–4 months of supplementation with a leucine-rich amino acid mixture significantly improved lean body mass in elderly people [51,52] with [51] or without [52] improvement in muscle strength and physical function. Only with a longer leucine-enriched essential amino acid mixture supplementation period (8–16 months), an improved 13–17% whole body lean mass in all areas (legs, arms and trunk tissues) associated with an amelioration of muscular strength and performance has been described in healthy elderly people [53]. These data suggested that improvement in lean body mass in elderly was more marked with a very long-term leucine-enriched amino acid mixture than with a high dose of leucine alone.

Except the recent study of Verhoeven *et al.* [47\*\*], long-term free leucine supplementation in elderly has not been investigated; thus, it is not possible to definitively conclude on the efficacy of leucine *per se* to counteract or prevent sarcopenia. However, taken together, the experiments with enriched leucine amino acid mixture supplementation both in rats and humans suggested that improvement in lean body mass and/or muscle mass and strength needs very long-term supplementation to translate into beneficial modification of body composition in elderly.

Another strategy based on the improvement in muscle protein anabolism sensitivity to normal daily leucine intake in elderly has been suggested. Indeed, the defect in leucine or food-stimulated muscle protein anabolism in old rats may be reversed when supplemented with antioxidants [54] or NSAIDs [55].

## Conclusion

Although it is evident that leucine is able to stimulate muscle protein synthesis through activation of the mTOR signaling pathway, its efficacy to improve muscle mass in various physiological conditions is still controversial because several studies have led to contradictory results. However, to our opinion, some factors must be considered to explain these discrepancies before withdrawing nutritional strategies based on leucine supplementation. First, leucine supplementation is known to induce a decrease in both valine and isoleucine concentrations that is visible as soon as the first leucine-supplemented meal is given [40]. To prevent the fall of plasma valine and isoleucine concentrations induced by leucine excess, the 'leucine meal' should also be supplemented with valine and isoleucine. With chronic leucine supplementation, this adjustment may be tricky to perform to avoid imbalanced BCAA levels which would antagonize the anabolic effect of leucine. Second, when free leucine is added in a diet, it is rapidly absorbed and its plasma concentration increases before that of the other amino

acids coming from the digestion of the proteins present in the diet. Then, muscle protein synthesis machinery may be activated by this leucine increase (via mTOR activation) but cannot translate into protein synthesis because of the lack of simultaneous availability of the other amino acids (as substrates for protein synthesis). Thus, it may explain that whey proteins (leucine-rich proteins) or leucine-enriched amino acid mixture are often shown to be more efficient than leucine supplementation alone, due to the increase of leucine along with all other amino acids. Third, to be efficient, a leucine supplementation should be performed when a decreased response and/or sensitivity of protein anabolism to leucine has been observed. Depending on the physiological or pathological states, the 'leucine resistance' of protein metabolism may vary and, thus, condition the leucine amount to be used to overcome this resistance. And finally, although the anabolic effect of leucine is maintained after supplementation for 10 days in rodents [41,42], it could not be excluded that this effect may be abolished during long-term leucine supplementation. Indeed, we observed that a 'pulsed protein diet' was efficient to increase nitrogen balance within 15 days [56] but not anymore after a month (personal communication). Then, alternative periods of leucine-supplemented and nonsupplemented diets on a chronic basis might represent the appropriate nutritional strategy based on leucine anabolic properties.

Until now, rare are the studies that investigated the effect of long-term leucine supplementation on whole body composition either in rodents or humans. We think that all the points mentioned above should be taken into account when testing leucine as a nutritional tool. Moreover, a number of studies reported that activation of the mTOR/S6K1 pathway by leucine can exert inhibition on the early steps of insulin signaling leading to insulin resistance on glucose metabolism [57–60]. It, thus, appeared that it will be important in the future to determine whether chronic dietary leucine elevation could be beneficial in healthy individuals without deleterious effects such as increased fat mass and glucose intolerance due to alteration in insulin signaling.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 347).

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