Prolonged Leucine Supplementation Does Not Augment Muscle Mass or Affect Glycemic Control in Elderly Type 2 Diabetic Men1–3

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Abstract

The loss of muscle mass with aging has been, at least partly, attributed to a blunted muscle protein synthetic response to food intake. Leucine coingestion has been reported to stimulate postprandial insulin release and augment postprandial muscle protein accretion. We assessed the clinical benefits of 6 mo of leucine supplementation in elderly, type 2 diabetes patients. Sixty elderly males with type 2 diabetes (age, 71 ± 1 y; BMI, 27.3 ± 0.4 kg/m²) were administered 2.5 g L-leucine (n = 30) or a placebo (n = 30) with each main meal during 6 mo of nutritional intervention (7.5 g/d leucine or placebo). Body composition, muscle fiber characteristics, muscle strength, glucose homeostasis, and basal plasma amino acid and lipid concentrations were assessed prior to, during, and after intervention. Lean tissue mass did not change or differ between groups and at 0, 3, and 6 mo were 61.9 ± 1.1, 62.2 ± 1.1, and 62.0 ± 1.0 kg, respectively, in the leucine group and 62.2 ± 1.3, 62.2 ± 1.3, and 62.2 ± 1.3 kg in the placebo group. There also were no changes in body fat percentage, muscle strength, and muscle fiber type characteristics. Blood glycosylated hemoglobin did not change or differ between groups and was 7.1 ± 0.1% in the leucine group and 7.2 ± 0.2% in the placebo group. Consistent with this, oral glucose insulin sensitivity and plasma lipid concentrations did not change or differ between groups. We conclude that prolonged leucine supplementation (7.5 g/d) does not modulate body composition, muscle mass, strength, glycemic control, and/or lipemia in elderly, type 2 diabetes patients who habitually consume adequate dietary protein. J. Nutr. doi: 10.3945/jn.111.138495.

Introduction

Aging is accompanied by a progressive decline in skeletal muscle mass and strength, termed sarcopenia (1). The progressive loss of skeletal muscle mass and strength results in a decline in functional capacity and predisposes to the development of chronic metabolic diseases, like obesity and type 2 diabetes (2). One of the major causes of sarcopenia seems to be the disruption in the regulation of muscle protein turnover. Recent work indicates that the elderly are less sensitive to the main anabolic stimuli, such as physical activity and/or food intake (3, 4). It has been suggested that increasing the leucine content of a meal can effectively compensate for the blunted muscle protein synthetic response to food intake in the elderly (5, 6). Recently, Katsanos et al. (5) reported that increasing the leucine content of an amino acid mixture (from 26 to 41%) normalizes the muscle protein synthetic response in the elderly when compared with young individuals. These findings were supported by Rieu et al. (6), who observed considerably higher postprandial muscle protein synthetic rates in elderly men after they consumed leucine-enriched meals. As a consequence, it has been suggested that increasing the leucine content of a meal represents an effective dietary strategy to augment the muscle protein synthetic response to food intake in the elderly.

So far only a single placebo-controlled study has been performed to evaluate the proposed clinical relevance of prolonged leucine supplementation in the elderly. We recently reported the impact of 3 mo of leucine supplementation with each main meal on muscle mass and strength in healthy, elderly males (7). No changes in skeletal muscle mass or strength were observed over the 3-mo intervention period. In response, some suggested that the absence of any impact of leucine supplementation on muscle mass and strength could be attributed to the relatively short intervention period and/or to the specific inclusion of healthy, elderly males. As such, we concluded that the impact of prolonged leucine supplementation should be assessed in more compromised elderly subpopulations over a more extensive intervention period (7).
It has been well established that elderly, type 2 diabetic patients generally have a more pronounced decline in skeletal muscle mass and/or strength compared with age-matched, normoglycemic controls (2). Because of this accelerated loss of muscle mass (8), it would be of particular interest to study the impact of leucine supplementation on muscle mass in this specific elderly subpopulation. Furthermore, amino acids (and leucine in particular) act as strong stimuli for endogenous insulin release by the pancreatic β-cell (9, 10). Leucine coingestion has been reported to effectively increase postprandial insulin release, stimulate glucose disposal, and subsequently improve glycemic control in type 2 diabetes patients (11–13). In addition, recent work in rodents reported substantial improvements in blood lipid profiles following prolonged leucine supplementation (14). Consequently, prolonged leucine supplementation may represent an even more effective nutritional strategy to increase muscle mass and improve glycemia and lipidemia in type 2 diabetes patients.

Prolonged intervention studies investigating the clinical benefits of leucine supplementation in elderly and/or type 2 diabetes patients are thus far lacking. Therefore, we assessed the impact of 6 mo of leucine supplementation with each main meal (7.5 g/d) on muscle mass and strength, body composition, insulin sensitivity, glycemia, and lipidemia in a large group of elderly, type 2 diabetes patients (71 ± 1 y). This is the first study to our knowledge to assess the clinical relevance of such prolonged leucine supplementation in vivo in humans.

Methods

Participants. A total of 60 elderly men with type 2 diabetes were selected to participate in a 6-mo (24 wk) nutritional intervention program. For all participants, medical history was evaluated and an oral glucose tolerance test (OGTT)9 was performed prior to inclusion. An electrocardiogram was performed at rest and during submaximal exercise. Exclusion criteria included (silent) cardiac or peripheral vascular disease, orthopedic limitations, and/or impaired renal function. Participants were treated with either dietary recommendation only (n = 6) or oral blood glucose-lowering medication: metformin combined with sulfonylurea derivatives and/or thiazolidinediones (n = 21), metformin only (n = 28), or sulfonylurea derivatives only (n = 5). All participants were receiving stable medication and/or dietary prescriptions for at least 3 mo before the intervention. All eligible men were randomly assigned to either the leucine- or placebo-supplemented group. Three participants dropped out for medical reasons not related to the study. Participants’ characteristics are provided in Table 1. All participants were informed about the nature and possible risks of the experimental procedures before their written informed consent was obtained. The study was performed according to the principles of the Declaration of Helsinki and was approved by the local Medical Ethical Committee.

Study design. Participants ingested either 2.5 g leucine or a placebo after each main meal (breakfast, lunch, and dinner) during the entire 24-wk intervention period. Anthropometrics (height, body weight, waist:hip ratio), muscle strength [one repetition maximum (1RM)], and body composition (DXA) were assessed and muscle biopsies, blood samples, and dietary intake and physical activity records were collected before, after 12 wk, and after cessation of the nutrition intervention program.

9 Abbreviations used: CSA, cross-sectional area; EAA, essential amino acid; HbA1c, blood glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; MET, mean equivalent task; NEAA, nonessential amino acid; OGIS, oral glucose insulin sensitivity; OGTT, oral glucose tolerance test; 1RM, 1 repetition maximum; TAA, total amino acid.

Diet and physical activity. Standardized meals were provided to all participants the evening prior to each test day. The participants were instructed to refrain from strenuous physical activity for at least 3 d prior to testing. On all test days, participants arrived at the laboratory by car or public transportation following an overnight fast. To assess potential changes in habitual daily food intake and physical activity during the 6-mo intervention period, the participants recorded 3-d weighted dietary intake records and 2-d physical activity records. Dietary intake was recorded before and after 3, 7, 11, 15, 19, and 23 wk of intervention (Komeet, 4,059 BaS Nutrition Software). Habitual physical activity was recorded before and after 11 and 23 wk of intervention. For every type of activity, a mean equivalent task (MET) score was assigned as previously defined (15). Energy expenditure was calculated as mean MET-h/d (16).

Supplementation. All participants were studied over a 24-wk intervention period during which they were supplemented with either 7.5 g/d l-leucine (Frutarom) or a placebo (wheat flour; Verstegen). The participants ingested 5 capsules (500 mg each) after each main meal (breakfast, lunch, and dinner). The supplements were provided in a double-blind manner and the different capsules could not be distinguished by scent, color, or taste.

Muscle strength. Maximal strength was assessed by 1RM strength tests on leg-press and leg-extension machines (Technogym). During a familiarization trial, the proper lifting technique was demonstrated and practiced, after which maximal strength was estimated by using the multiple repetitions testing procedure (17). In an additional session, at least 1 wk prior to muscle biopsy collection, each participant’s 1RM was determined as previously described (18). The 1RM test was repeated after 12 wk and after the cessation of the intervention program.

Body composition. Body composition and bone mineral content were measured with DXA (Hologic, Discovery A, QDR Series). Anthropometrics were measured by trained observers using standard techniques (19).

Blood samples. Before, and after 4, 8, 12, 16, 20, and 24 wk of intervention, blood samples were collected from fasting subjects to determine basal plasma glucose and insulin concentrations, plasma amino acid and lipid profiles, serum creatinine, and blood glycosylated hemoglobin (HbA1c) content. Blood (10 mL) was collected into EDTA-containing and serum tubes. EDTA tubes were immediately centrifuged at 1000 × g for 10 min at 4°C (plasma) and the serum tubes were centrifuged at 1000 × g for 15 min at 21°C (serum) after allowing the blood to clot for 90 min at 21°C. Aliquots of plasma and serum were immediately frozen in liquid nitrogen and stored at −80°C until further analysis. Plasma glucose concentrations were analyzed with a COBAS FARA analyzer (Uni Kit III; Roche). Plasma insulin concentrations were determined by using an Insulin RIA kit (LINCO Research). Plasma free amino acid concentrations were analyzed with a dedicated amino acid analyzer (LCA10; Shimadzu Benelux) as previously described (7). Reagents to determine plasma TG, total cholesterol, and HDL-
chondrocytes were from ABX Diagnostics. Plasma FFA concentrations were analyzed with the NEFA C test kit from Wako Chemicals. Because plasma TG concentrations were <4.5 mmol/L, LDL-cholesterol could be calculated by LDL cholesterol = total cholesterol − HDL cholesterol − TG/2.2 (in mmol/L). Serum creatinine concentrations were determined using the Jaffe rate method on a Synchron LX Systems analyzer with a Synchron creatinine reagent kit (Beckmann Coulter). Blood HbA1c content was analyzed by HPLC (Bio-Rad Variant II 4).

Whole-body insulin sensitivity. Whole-body insulin sensitivity and/or oral glucose tolerance were assessed by fasting blood glucose and insulin concentrations using the homeostasis model assessment of insulin resistance (HOMA-IR) (20). Furthermore, the oral glucose insulin sensitivity (OGIS) index (21) and the insulin sensitivity index (ISI) (22) were calculated from the data derived from the OGTT.

Muscle biopsies. Three days prior to the onset of nutritional intervention, after 12 wk of intervention and immediately after cessation of the nutritional intervention, skeletal muscle biopsies were taken from the right leg of each participant. After local anesthesia was induced, percutaneous needle biopsy samples (50–80 mg) were collected from the vastus lateralis muscle, ~15 cm above the patella (23). Any visible nonmuscle tissue was removed immediately and biopsy samples were embedded in Tissue-Tek (Sakura Finetek), frozen in liquid nitrogen-cooled isopentane, and stored at −80°C until analyses.

Muscle tissue analysis. From all biopsies, 5-μm-thick cryosections were cut at −20°C. All samples from each participant were mounted together on uncoated glass slides. Cross-sections were stained for muscle fiber typing using the analytical procedures previously described (24). In short, muscle fiber typing (type I vs. IIA vs. IIX) was determined based on staining with antibodies against MHC-I and MHC-IIA, and anti-laminin was used to visualize the basement membrane. After staining, all images were digitally captured by using fluorescence microscopy (Nikon Instruments Europe). Image processing and quantitative analyses were performed as previously described (25). Within each image, the number of fibers and the muscle fiber cross-sectional area (CSA) were measured for the type I, IIA, and IIX fibers separately.

24-h Urine collection. To determine urinary nitrogen and creatinine excretion, 24-h urine was collected over the last day of the 3-d dietary intake assessment as previously described (25). Nitrogen content was analyzed with an elemental analyzer (model CHN-ORAPID, Heraeus). Total nitrogen excretion was calculated from total urinary nitrogen analyzed with an elemental analyzer (model CHN-ORAPID, Heraeus). Nitrogen content was calculated from urinary nitrogen loss (26). Nitrogen balance was calculated as the difference between nitrogen intake assessment as previously described (25). Total nitrogen excretion was calculated from total urinary nitrogen analyzed with an elemental analyzer (model CHN-ORAPID, Heraeus). Nitrogen content was calculated from urinary nitrogen loss (26). Nitrogen balance was calculated as the difference between nitrogen intake and/or output (27).

Statistical analysis. Data are expressed as means ± SEM. Baseline characteristics between groups were compared by means of an independent samples t test. Pre- vs. 3 mo vs. postintervention data were analyzed using repeated-measures ANOVA with time as within-subjects factor and treatment as between-subjects factor. For muscle fiber type analyses, a second within-subjects factor (type I vs. type II fibers) was included. In case of significant main effects or interactions, post hoc testing with Bonferroni correction and/or separate analyses within groups were performed when appropriate. Significance was set at P < 0.05. All calculations were performed using SPSS 15.0.

Results

Participants. A total of 57 men completed the intervention study, 28 in the placebo group and 29 in the leucine group. Baseline variables did not differ between groups (Table 1). Participants had been diagnosed with type 2 diabetes for 3 ± 1 y. Except for 1 patient in the leucine group, no changes in medication dose occurred during the 6-mo intervention period.

Diet and physical activity. Analysis of the 3-d dietary intake records collected before, during, and after 24 wk of intervention did not differ in total daily energy intake between groups or change over time (Supplemental Table 1). In addition, the macronutrient composition of the diet did not change over time and did not differ between groups (Supplemental Table 1). Daily protein intake prior to the supplementation period did not differ between the placebo (0.94 ± 0.04 g/kg body weight) and leucine (1.04 ± 0.05 g/kg body weight) groups and did not change throughout the supplementation period (Supplemental Table 1). Habitual physical activity levels and mean energy expenditure at baseline did not differ between the placebo (1.55 ± 0.03 MET-h/d) and leucine (1.55 ± 0.04 MET-h/d) groups and did not change over time.

Muscle strength. At baseline, 1RM for leg press and leg extension did not differ between groups (Table 2). After 24 wk of intervention, muscle strength had increased in both the placebo and leucine groups for leg press (P < 0.001) and leg extension (P < 0.001), with no differences between groups.

Body composition. Whole-body and leg fat mass and fat-free mass did not differ between the groups prior to the intervention (Table 2). Throughout the intervention, body composition, fat mass, and lean mass did not change over time or differ between groups.

Glycemic control. Measures of glyemic control did not differ between the placebo and leucine groups prior to intervention (Table 3). After 24 wk of intervention, the basal fasting insulin concentration increased in both groups. In accordance, insulin resistance significantly increased over time as assessed by HOMA-IR and ISI. However, blood HbA1c values remained stable throughout the intervention period. Fasting blood glucose concentrations and the OGIS index did not change over time or differ between groups (Table 3).

Plasma lipids and urine analyses. Plasma lipid concentrations did not differ between groups prior to the intervention and did not change in either group (Supplemental Table 2). Serum lipid concentrations were within the normal range prior to intervention and did not change over time in either the placebo (from 99.0 ± 5.3 to 84.0 ± 5.3 μmol/L) or leucine (from 99.0 ± 3.5 to 94.6 ± 4.4 μmol/L) group, and the groups did not differ. Creatinine clearance at baseline did not differ between the placebo (75.8 ± 3.2 mL/min per 1.73 m²) and leucine (82.2 ± 3.7 mL/min per 1.73 m²) groups and did not change in either group. Prior to intervention, 24-h nitrogen balance was −1.2 ± 0.62 g/d in the placebo group and −0.52 ± 0.54 g/d in the leucine group and did not change in either group.

Amino acid profiles. Plasma total amino acid (TAA), nonessential amino acid (NEAA), and essential amino acid (EAA) concentrations in fasting men did not differ between groups and did not change in either group (Table 4). For the plasma BCAA, there were significant time × treatment interactions. Basal plasma leucine concentrations increased in the leucine group by 13 ± 3% within 12 wk of supplementation (P < 0.05), after which concentrations remained elevated. The 2 other BCAA, valine and isoleucine, decreased over time in the
leucine group. Basal plasma valine concentrations declined by 23 ± 2% within 4 wk of supplementation (P < 0.05), after which concentrations remained stable. Basal plasma isoleucine concentrations declined by 16 ± 2% within 4 wk of supplementation (P < 0.05), after which concentrations remained stable. Plasma BCAA concentrations did not change in the placebo group (Table 4).

Muscle tissue analysis. Type I and II muscle fiber percentage did not differ between groups prior to the intervention (Supplemental Table 3). Type I muscle fiber percentage was 43 ± 2, 43 ± 2, and 48 ± 2% at 0, 3, and 6 mo for the entire group, with no changes over time. Muscle fiber CSA at baseline did not differ between the placebo and leucine groups for the type I, type IIa, or type IIx fibers and the values did not change during the intervention. Muscle fiber CSA at baseline did not differ between the placebo and leucine groups for the type I, type IIa, or type IIx fibers and the values did not change during the intervention. Notably, type II muscle fiber CSA or type IIx fibers and the values did not change during the intervention.

Discussion
The present study shows that 6 mo of leucine supplementation (a total of 7.5 g/d) with each main meal does not augment skeletal muscle mass and strength, modulate body composition, or improve glycemic control and blood lipid profile in elderly men with type 2 diabetes who habitually consume sufficient protein. Aging is associated with the gradual but progressive loss of skeletal muscle mass and function, resulting from an imbalance between muscle protein synthesis and breakdown. Recent work from Katsanos et al. (5) and Rieu et al. (6) shows that increasing the leucine content of a meal increases the postprandial muscle protein synthetic response in healthy elderly men. Consequently, it has been suggested that long-term leucine supplementation with each main meal represents an effective nutritional intervention strategy to stimulate postprandial net muscle protein accretion and, as such, increase muscle mass and strength in the elderly (28). Katsanos et al. (5) reported a substantial 0.008%/h increase in postprandial muscle protein synthesis rate for up to 2.5 h after increasing the leucine content of an oral amino acid mixture. Extrapolation of these data toward the impact of prolonged leucine supplementation with each main meal should theoretically result in an enormous 3.4 kg (range 2.8–4.2 kg) gain in muscle mass over a 6-mo intervention period. Consequently, such a ~4–6% increase in whole-body lean tissue mass could be expected in the leucine-supplemented group. The latter would easily be detected by DXA scanning as applied in the present study (with a CV for lean tissue mass < 0.5%). However, even after 6 mo of leucine supplementation, we did not observe any effect on muscle mass (Table 2) and/or muscle fiber size (Supplemental Table 3). It seems evident that the suggested increase in muscle protein synthesis in the postprandial phase following leucine supplementation cannot be translated into

TABLE 2  Body composition and muscle strength during 24 wk of leucine or placebo intervention in diabetic men

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n = 28</th>
<th></th>
<th>Leucine, n = 29</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>wk 0</td>
<td>wk 12</td>
<td>wk 24</td>
<td>wk 0</td>
</tr>
<tr>
<td>Body composition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>84.6 ± 2.0</td>
<td>85.0 ± 2.0</td>
<td>85.1 ± 2.1</td>
<td>83.6 ± 1.8</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>62.2 ± 1.3</td>
<td>62.2 ± 1.3</td>
<td>62.2 ± 1.3</td>
<td>61.9 ± 1.1</td>
</tr>
<tr>
<td>Fat, %</td>
<td>21.8 ± 0.7</td>
<td>23.3 ± 0.9</td>
<td>23.4 ± 0.9</td>
<td>22.5 ± 0.6</td>
</tr>
<tr>
<td>Bone mineral content, kg</td>
<td>2.7 ± 0.1</td>
<td>2.7 ± 0.1</td>
<td>2.7 ± 0.1</td>
<td>2.7 ± 0.1</td>
</tr>
<tr>
<td>Leg lean mass, kg</td>
<td>19.3 ± 0.8</td>
<td>19.4 ± 0.5</td>
<td>19.4 ± 0.4</td>
<td>19.0 ± 0.4</td>
</tr>
<tr>
<td>Leg fat mass, kg</td>
<td>5.0 ± 0.3</td>
<td>5.1 ± 0.3</td>
<td>5.2 ± 0.3</td>
<td>4.8 ± 0.2</td>
</tr>
<tr>
<td>Muscle strength</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Leg press, kg</td>
<td>205 ± 7</td>
<td>210 ± 8*</td>
<td>218 ± 8*#</td>
<td>202 ± 7</td>
</tr>
<tr>
<td>Leg extension, kg</td>
<td>88 ± 3</td>
<td>91 ± 3*</td>
<td>94 ± 4*#</td>
<td>80 ± 2</td>
</tr>
</tbody>
</table>

1 Values are mean ± SEM. *Different from wk 0, P < 0.05, #different from wk 12, P < 0.05.

TABLE 3  Glycemic control during 24 wk of leucine or placebo intervention in diabetic men

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n = 28</th>
<th></th>
<th>Leucine, n = 29</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>wk 0</td>
<td>wk 12</td>
<td>wk 24</td>
<td>wk 0</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>7.5 ± 0.2</td>
<td>7.3 ± 0.2</td>
<td>7.6 ± 0.3</td>
<td>8.0 ± 0.2</td>
</tr>
<tr>
<td>Glucose 120 min, OGTT, mmol/L</td>
<td>13.9 ± 0.8</td>
<td>14.1 ± 0.9</td>
<td>14.5 ± 0.8</td>
<td>13.7 ± 0.8</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.2 ± 0.2</td>
<td>7.2 ± 0.2</td>
<td>7.2 ± 0.1</td>
<td>7.1 ± 0.1</td>
</tr>
<tr>
<td>Plasma insulin, pmol/L</td>
<td>103 ± 7</td>
<td>113 ± 15</td>
<td>144 ± 18*#</td>
<td>95 ± 6</td>
</tr>
<tr>
<td>Insulin 120 min, OGTT, pmol/L</td>
<td>465 ± 60</td>
<td>495 ± 76</td>
<td>506 ± 82*#</td>
<td>383 ± 72</td>
</tr>
<tr>
<td>Insulin peak, pmol/L</td>
<td>641 ± 99</td>
<td>634 ± 102</td>
<td>775 ± 101*#</td>
<td>486 ± 72</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.8 ± 0.4</td>
<td>5.1 ± 0.7</td>
<td>6.8 ± 0.9*#</td>
<td>4.7 ± 0.3</td>
</tr>
<tr>
<td>ISI</td>
<td>2.5 ± 0.2</td>
<td>2.7 ± 0.3</td>
<td>2.0 ± 0.2*#</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>OGTT</td>
<td>350 ± 9</td>
<td>352 ± 8</td>
<td>345 ± 8</td>
<td>338 ± 8</td>
</tr>
</tbody>
</table>

1 Values are mean ± SEM. *Different from wk 0, P < 0.05, #different from wk 12, P < 0.05.
muscle mass accrual during a more prolonged dietary intervention. This appears to be consistent with previous findings from our group in which leucine supplementation did not affect body composition in healthy elderly males over a 3-mo intervention period (7). It was suggested that the duration of the latter study might have been insufficient to detect any clinically relevant improvements. In addition, it was suggested that leucine coingestion with each main meal would be of more benefit to more compromised elderly subpopulations as opposed to healthy elderly men (7). Therefore, in the present study, we implemented 6 mo of dietary supplementation in elderly, type 2 diabetes patients. The peripheral insulin resistance observed in type 2 diabetes patients is likely to further attenuate the postprandial muscle protein synthetic response to food intake (29) and could be largely responsible for the accelerated loss of muscle mass with aging in these patients (30). Nonetheless, we did not observe any increase in muscle mass and/or function after 3 and 6 mo of nutritional intervention in these elderly type 2 diabetes patients (Table 2). As such, we must conclude that even such long-term leucine supplementation does not represent an effective nutritional strategy to increase muscle mass and function.

Apart from its proposed role in regulating postprandial muscle protein synthesis, leucine also acts as a strong insulin secretagogue (31–33). The latter has since been applied as an effective nutritional strategy to augment postprandial insulin release, increase blood glucose disposal, and, as such, improve glycemic control in type 2 diabetes patients (11–13, 34). Furthermore, Zhang et al. (14) also reported a reduction in diet-induced obesity, hyperglycemia, and hypercholesterolemia following prolonged leucine supplementation in mice fed a high-fat diet. In the present study, we assessed the impact of prolonged leucine coingestion with each main meal on oral glucose tolerance and macronutrient composition of the diet during the intervention period (7). The latter showed no changes in daily energy intake and/or macronutrient composition of the diet during the intervention period in either the placebo and leucine-supplemented group. Mean habitual dietary protein intake was 0.94 ± 0.05 g · kg⁻¹ · d⁻¹ and 1.04 ± 0.05 g · kg⁻¹ · d⁻¹ in the placebo and leucine-supplemented groups and remained stable throughout the intervention. Daily protein intake values are in line with dietary guidelines (36–39) and indicate that the diabetes patients ingested sufficient dietary protein. It could be speculated that habitual dietary protein consumption may have provided sufficient leucine to optimize postprandial muscle protein synthesis, making the impact of additional leucine supplementation with each main meal of no surplus benefit. The habitual physical activity level did not change over time or between groups. With a mean energy expenditure of ~1.5 MET·h/d, these elderly patients seemed to be more active compared with diabetes patients in the US (16) but less active compared with patients in Canada (16). Whether different leucine supplementation intervention strategies, e.g., different timing of leucine ingestion around the main meals and/or in combination with an exercise/physical activity regimen, result in greater clinical benefits remains to be established. Prolonged supplementation with relatively large amounts of leucine did not seem to be accompanied by any negative side effects. Supplements were well tolerated.
tolerated and there were no complaints of gastro-intestinal discomfort reported. Because excess dietary protein intake has been associated with an increased risk of developing renal failure, we also measured serum creatinine and urinary creatinine excretion to assess potential changes in kidney function. Because no changes were observed in serum creatinine levels and 24 h creatinine clearance in either group, prolonged leucine supplementation (7.5 g/d) does not seem to have any negative impact on renal function.

In this study, we show that the proposed stimulating properties of co-ingesting leucine on postprandial muscle protein synthesis rates do not translate into muscle mass accrual during more prolonged nutritional intervention. Six months of leucine supplementation (7.5 g/d) does not augment muscle mass and strength, improve blood glucose homeostasis, and/or lipid profile in elderly type 2 diabetes patients. In conclusion, leucine supplementation after each main meal does not represent an effective nutritional strategy to increase muscle mass or strength or to improve glycemic control or circulating lipids in elderly, type 2 diabetic men who habitually consume adequate dietary protein.

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Literature Cited


