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Review

Effects of acute oral feeding on protein metabolism and muscle protein synthesis in individuals with cancer

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ABSTRACT

Weight loss and muscle loss are common in individuals living with cancer, with ≤50% experiencing involuntary weight loss at any time point in their cancer journey, and between 11% and 74% having sarcopenia or significant muscle loss. These changes in body composition are related to poor outcomes such as increased treatment toxicity, impaired quality of life, and reduced survival duration. Poor outcomes are not restricted to those who are underweight with severe weight loss; sarcopenia alone has been shown to be a prognostic marker across all body mass index categories, ranging from underweight to obesity To understand the mechanism of nutrition interventions in cancer and to develop effective future interventions, it is necessary to look at the acute effects of feeding on the response of the body and the ability to reach an anabolic response. The aim of this study was to explore and summarize the emerging evidence on metabolic effects of acute oral interventions on whole body protein kinetics and muscle protein synthesis in individuals with cancer.

Introduction

Weight loss and muscle loss are common in individuals living with cancer, with ≤50% experiencing involuntary weight loss at any time point in their cancer journey [1], and between 11% and 74% having sarcopenia or significant muscle loss [2,3]. These changes in body composition have been related to poor outcomes such as increased treatment toxicity, impaired quality of life (QoL), and reduced survival duration [4,5]. Poor outcomes are not restricted to those who are underweight with severe weight loss; sarcopenia alone has been shown to be a prognostic marker across all body mass index categories, ranging from underweight to obesity [5].

Several mechanisms behind weight loss and muscle wasting in cancer have been identified, such as systemic inflammation, tumor-induced metabolic alterations, inadequate dietary protein intakes, and physical activity levels, poly-pharmacy, or a combination of these [6,7]. We recently showed that a higher protein turnover and muscle protein breakdown in patients with cancer was evident when compared with matched healthy controls, and that protein turnover and muscle breakdown were associated with muscle weakness and impaired physical function [8].

So far, the main nutritional strategy to prevent or treat muscle wasting in patients with cancer has been the adequate provision of dietary energy and substrates, such as macronutrients, mainly protein. Amino acids from protein are required for muscle protein synthesis. Several studies in humans show that 20 to 35 g of a high-quality protein is required to reach maximal muscle protein synthesis [9,10]. Higher amounts (i.e., 70 g of dietary protein intake) result in greater reduction in whole body protein breakdown than a 40-g dietary protein intake, and this will positively affect protein anabolism [10].

To achieve this, the main strategy to optimize dietary intake is nutritional counseling, with or without the provision of oral nutritional supplements (ONS), enteral nutrition, or parenteral nutrition. However, despite the positive results of these strategies on dietary intake and body weight, results on muscle mass, QoL, and clinical outcomes are not convincing. A recent meta-analysis indicated an overall benefit of ONS on body weight during chemo(radio)therapy, and ONS enriched with ω-3 polyunsaturated fatty acids (PUFAs) showed attenuation of lean body mass (LBM) loss and improvement

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of some QoL domains, but no conclusions could be drawn on treatment toxicity or survival [11]. Moreover, in advanced stages of cancer, patients could become "refractory cachectic" meaning that nutrition interventions are not effective due to progressive disease and cachexia [12]. By using stable isotope technologies in an acute study design (5 h), Deutz et al. showed that a high-leucine ONS containing ω-3 PUFAs and β-hydroxy-β-methylbutyrate (HMB) in people with advanced cancer was significantly more effective in stimulating muscle protein synthesis, whereas a conventional ONS did not change muscle protein synthesis [13]. Engelen et al. showed that an anabolic response was reached after oral intake of 14 g of essential amino acids (EAA) and leucine caused an anabolic response in patients with advanced lung cancer [14]. Other studies have shown potential benefits of HMB and EAA mixtures in malnourished older adults [15] and in hospitalized older adults with chronic obstructive pulmonary disease (COPD), chronic heart failure (HF), acute myocardial infarction, or pneumonia [16].

To understand the mechanism of nutrition interventions in cancer and to develop effective future interventions, it is necessary to look at the acute effects of feeding on the response of the body and the ability to reach an anabolic response. This study will explore and summarize the emerging evidence on metabolic effects of acute oral interventions on whole body protein kinetics and muscle protein synthesis in individuals with cancer.

The role of acute oral feeding in cancer

This review focuses on the effects of acute (<24 h) oral feeding on protein metabolism in cancer. Protein metabolism includes muscle protein synthesis, muscle protein breakdown, and the anabolic response to feeding. Kim et al. defined the anabolic response as "the difference between protein synthesis and protein breakdown, or the net protein balance, in response to ingestion of protein or a meal containing protein. It usually refers to gain of muscle protein but can involve the entire body" [10].

Muscle protein balance in the human body is controlled by many signaling pathways, including an anabolic arm reliant on growth factors and nutrient signaling via (among others) the mammalian target of rapamycin (mTOR) pathway. The catabolic arm involves signaling cascades connected to autophagy genes and ubiquitin-mediated proteasomal degradation of myofibrils [17]. Within the anabolic arm, the right amount and type of amino acids from dietary protein are required to achieve muscle protein synthesis. It is well known that oral amino acids stimulate skeletal muscle anabolism in healthy individuals [10], as well as in individuals with diseases such as COPD [18] and cancer [14]. There are age-related differences in the anabolic response, with older individuals needing more amino acids than young adults to reach a comparable anabolic response, and in sick people there could be a higher breakdown, lower protein synthesis, or both, affecting the net protein balance and anabolic response to protein [9].

Acute metabolic response to oral feeding

A handful of metabolic studies have investigated the effects of acute oral feeding in people with cancer, utilizing oral amino acids, ONS, or meals (see Table 1).

One of the first studies investigating the effects of oral amino acids on muscle protein anabolism in cancer was conducted by Dillon et al. [19]. In six women with ovarian cancer receiving chemotherapy who showed evidence of systemic inflammation and weight loss, 18 oral boluses of 2.22 g amino acids (in total 40 g of amino acids, of which 18 g were EAAs) significantly decreased protein breakdown, which resulted in an improved net muscle protein synthesis. Engelen et al. investigated the metabolic effects of two amino acid mixtures in lung cancer [14]. In 13 people with non-small cell lung cancer (NSCLC) with systemic inflammation, and critical weight loss in 38% of the group, 14 g of a free EAA mixture induced a higher protein synthesis and net protein anabolism than a regular whey protein mixture of EAA and non-EAA. Interestingly, leucine from the free EAA mixture did not contribute to the anabolic response. There was a positive correlation between net protein anabolism and the amount of EAA consumed, as well as the EAA appearance in the systemic circulation. This correlation was independent of weight loss, systemic inflammatory response, or length of survival.

Standardized drinks containing protein, fat, and carbohydrates, also known as ONS, often are prescribed to enrich the diet of patients with cancer. Several studies applied ONS in metabolic studies in individuals with cancer. Early work from Barber et al. looked at albumin and fibrinogen synthesis rates in individuals with pancreatic cancer (n = 8) and healthy controls (n = 6), and showed that in both groups, protein synthesis rates were upregulated during consumption of hourly sips of an ONS for 4 h [20]. In a mixed group of individuals with cancer, the use of ONS high in EAA and ω-3 PUFAs was shown to increase muscle protein buildup significantly better than conventional supplements [13].

In a small group of patients with pancreatic cancer and signs of cachexia, sips of ONS were consumed over 4 h. In this study, net protein synthesis in response to the sip feeding was similar between patients with cancer and healthy individuals; however, protein breakdown was decreased in pancreatic cancer only, whereas protein synthesis was stimulated and breakdown decreased in healthy controls [21]. In a cohort of women with stage II breast cancer, protein synthesis was assessed before and within 24 h after mastectomy surgery. Surgery was shown to upregulate fasted protein synthesis and breakdown rates, and reduce net protein catabolism [22].

We retrieved two studies from the 1980 to 1990s that investigated short-term effects of meals or standardized diets on anabolic response. One study applied identical food intake for 2 d, both preoperatively and postoperatively, in colorectal cancer: ad libitum on day 1 and six equal portions every 2 h during the experimental period [23]. No significant differences in rates of nitrogen flux, protein synthesis, or protein breakdown were found before and after tumor resection. Both before and after tumor resection, nitrogen balance was positive with levels varying between +0.98 and +2.55 g/24 h. The investigators estimated that 1 g nitrogen/24 h is required for 1 kg of lean mass buildup in 1 mo.

In non-cachectic patients with non-metastatic lung cancer compared with controls undergoing elective aneurysm surgery, whole body protein turnover and leucine oxidation were assessed during 4 h postabsorptive and 4 h of feeding. Four small hourly meals composed of bread, margarine, cheese, raisins, and milk were consumed by the participants. During feeding, leucine oxidation and incorporation into protein remained the same and release of leucine caused by protein breakdown dropped. Despite higher incorporation and release of leucine in cancer than in controls, the protein balance was not improved [24].

In a group of five individuals, four with lung and one with kidney cancer, hourly meals of a milk-based liquid diet were administered over 10 h as well as intravenous isotopes of leucine and sodium bicarbonate. Despite a comparable whole body protein synthesis and breakdown in the patients with cancer and healthy controls, muscle samples showed a significantly lower muscle protein synthesis in those with cancer than in healthy controls [25].

Although the studies cited here are small and heterogenous, all but one showed that patients with cancer are able to achieve protein anabolism in response to a high-protein meal or supplement.

Table 1
Amino acid kinetic studies assessing protein synthesis in response to oral feeding in patients with cancer

Study design	Cancer type	Nutritional status/Systemic inflammation	Study design	Type of oral feeding	Results	PS
Oral amino acids						
Dillon 2007 ORAL AA	Ovarian (stage IIIC) (n = 6)	- Weight loss: >10% in n = 6 (100%) - BMI: 22 ± 3 kg/m^2 - CRP: 7.7 ± ng/mL - >6 mo postsurgery	- n = 8 healthy older controls - Primed continuous IV of labeled PHE (prime: 2 μmol/kg, cont: 0.05 μmol·kg·min^{-1})	- 40 g AAs (18 g EAA and 22 g non-EAA) - Boluses (30 mL) every 10 min for 3 h (total: 540 mL) - Amount of AA resembling meat protein (based on Volpi, *ACJN* 2003)	- Skeletal muscle TNF-a, IL-6, NF-κB were elevated - Muscle FSR increased significantly - PB remained unchanged - PHE balance improved - AA were capable of stimulating MPS	MPS FSR
Engelen 2015 ORAL AA	NSCLC, advanced (stage III and IV) (n = 13)	- Weight loss: >5% weight loss in 3 to 6 mo in n = 5 (38%) - BMI: 26.5 ± 1.1 kg/m^2 - CRP: 9.8 ± 3.7 mg/L - >4 wk after cancer treatment	- n = 11 healthy age-matched controls - Randomized, double-blind, crossover design - Primed, constant, continuous IV of labeled PHE and TYR	- 250 mL non-caloric soft drink w L-^{15} N PHE with 30 g maltodextrin - E: 14 g of free EAA with high leucine levels (EAA/leucine) - C: 14 g balanced AA mixture with EAA + non-EAA (whey protein)	- Postabsorptive PS and PB comparable in cancer and controls - PS and net protein anabolism > after intake of EAA/leucine than C mixture ($P < 0.001$) in cancer and healthy individuals - Significant correlation between net protein anabolism and dietary EAA intake and EAA appearance in systemic circulation in cancer and health - Presence of muscle or recent weight loss, systemic inflammatory response, or length of survival did not influence this relationship - High leucine levels in EAA/leucine mixture: No anabolic benefit	WB
ONS						
Barber 2000 ORAL NS	Pancreatic (n = 8)	- Weight loss: 18.9 (12.7−37.5) - BMI: N/A - CRP: N/A, IL-6: E: 7.4 (3.5−32.3) vs C: 1.8 (1−3) pg/mL ($P < 0.005$) - >4 wk after cancer treatment	- n = 6 healthy controls - After 2 h of feeding: 2 h of IV [^{2} H$_5$] -PHE or [^{2} H$_8$]-PHE	ONS (1/12 of energy requirements (13% protein) on an hourly basis over 4 h	- Fasting albumin synthesis rates similar between E and C - Albumin synthesis rates rose on feeding by 29% and 24% in cancer and controls - Fasting fibrinogen synthetic rate: Higher in cancer than in controls (3.3 vs 1 g/d, $P = 0.0019$) - Acute-phase PS upregulated in cancer - Similar albumin synthesis in cancer and controls. Albumin synthesis and fibrinogen synthesis upregulated during feeding in both groups	
Deutz 2011 ONS	Mixed types (stage II to IV) (n = 25)	- Weight loss: 2.9% ± 2.2% - BMI: 25.1 ± 3.3 kg/m^2 - CRP: 28.7 ± 8.2 ng/mL - >4 wk after cancer treatment	- E: N = 13, C: N = 12 - Priming dose (2 mmol/kg) of L-[ring-13 C6] PHE, followed by a continuous (0.07 mmol·kg·min^{-1}) infusion - Muscle biopsy 2 and 5 h after start of IV	E: ONS, 2 * 200 mL 640 kcal, 40 g protein (27%), 24.2 g casein, 11.9 g whey, 4.16 g free leucine, 8.38 g fish oil (2.2 g of EPA and 1.1 g DHA), specific oligosaccharides - C: 2 * 200 mL conventional ONS (640 kcal, 24 g (15%) casein protein)	- Plasma leucine increased in E: 7.8 g, vs C: 2.0 g ($P < 0.001$) - Postabsorptive muscle protein FSR was similar in E and C - Absorptive MPS: 0.073 (SD 0.023) to 0.097 (SD 0.033) %/h ($P = 0.027$), C: No change: 0.073 (SD 0.022) to 0.065 (SD 0.028) %/h, $P > 0.05$.	MPS FSR
Van Dijk 2015 ONS	Pancreas (n = 8)	- Weight loss: >10% in n = 7 (88%) - BMI: 20 kg/m^2 - CRP: 8.3 (IQR: 4.2−31.3) mg/L - >4 wk after cancer treatment	- n = 7 healthy controls - Primed continuous IV infusion of L-ring-[2 H5]PHE and L-3,3 2 H2]TYR for 8 h - sip feeds with L-1[13 C-PHE]	- 480 mL water sips, 60 mL every 30 min - 480 mL sip feeds (ONS: 50 g casein, 5.25 g leucine. 60 mL every 30 min (4 h in total)	- Baseline: PB higher in E than in C (67.1 vs 45.8 μmol/kg LBM) - PB decreased during ingestion (45.5 in E vs 33.7 μmol/kg LBM) - Splanchnic extraction similar between E and C during feeding - PS higher in weight-losing E patients than in C at baseline - PS did not respond to sip feeding in E, in contrast	WB

(*continued on next page*)

Table 1 (*Continued*)

Study design	Cancer type	Nutritional status/Systemic inflammation	Study design	Type of oral feeding	Results	PS
					with C ($P = 0.018$): 58.4 vs 47.9 μmol/kg LBM) - Net protein balance comparable between E and C	
Engelen 2017 ONS	Breast (stage II) (n = 9)	- Weight loss: None - BMI: 28.5 ± 5.1 kg/m^2 - CRP: 3 mg/L - >4 wk after cancer treatment	- n = 9 healthy controls - Before and within 24 h after mastectomy surgery - Primed, constant, and continuous infusion of labeled PHE and TYR - ONS intake after 1.5 h of primed, continuous isotope infusion	ONS (240 kcal, 15 g protein) + 158.8 mg L-^{15} N PHE	- PS and net balance E > C ($P < 0.001$) - Major surgery resulted in an upregulation of postabsorptive PS and PB rates ($P < 0.001$) and lower net protein catabolism ($P < 0.05$) and was associated with insulin resistance and increased systemic inflammation ($P < 0.01$) - Net anabolic response to the meal was reduced after surgery ($P < 0.05$) but higher in cancer ($P < 0.05$) indicative of a more preserved meal efficiency - Significant positive correlation between net protein anabolism and AA appearance in systemic circulation, independent of the presence of non-cachectic early-stage breast cancer or surgery	WB
Oral meals						
Glass 1983 ORAL MEALS	Colorectal (n = 11)	- Weight loss: N = 6 (55%) - BMI: N/A - CRP: N/A - No previous cancer treatment	- Before and after tumor resection - Urinary secretion of 15 N in ammonia and urea over a 9-h period after an oral dose of [15 N]-glycine	Identical food intake for 2 d (ad libitum on day preceding the preoperative study, and six equal portions every 2 h during the experimental period	- No significant differences in rates of nitrogen flux, PS, and PB were found before and after tumor resection	WB
Emery 1984 ORAL MEALS	Lung (n = 4, kidney (n = 1)	- Weight loss: N = 5 (100%), average 10.1% ± 5.9% - BMI: N/A - CRP: N/A - No previous cancer treatment	- n = 7 healthy controls - IV prime (1 mg/kg) of ^{13} C L-leucine and ^{13} C sodium bicarbonate (0.08 mg/kg), constant infusion of carboxyl ^{13} C labeled L-leucine 1 mg·kg·h^{-1}).	Hourly meals of a milk-based liquid diet (two-thirds of normal daily intake of protein and energy over 10 h (0.4–0.8 g protein•kg•h^{-1}, 4–8 kJ•kg• h^{-1})	- PS in muscle was much lower in E than in C (0.198 ± 0.020 %/h vs 0.030 ± 0.007 %/h, $P = 0.01$) - No difference between E and C for whole body PS and PB	MPS WB
Melville 1990 ORAL MEALS	Lung (n = 9)	- Weight loss: N = 6 (67%) - BMI: 22.6 ± 2.8 kg/m^2 - CRP: N/A - No previous cancer treatment	- n = 9 control (elective aneurysm surgery) - Primed continuous infusion of [^{13} C]- leucine (2.3 μmol·kg·h^{-1} + prime dose of 1.9 μmol/kg)	4 hourly meals (bread, margarine, cheese, raisins, milk): 1/12 of daily energy expenditure	- Postabsorptive incorporation of leucine into protein: Higher in E (102 ± 21 vs 86 ± 8) $P < 0.05$ - Release of leucine by protein degradation higher in E: 126 ± 19 vs 110 10 μmol/kg LBM/h $P < 0.01$), no differences for leucine oxidation - During feeding, incorporation of leucine into protein (106 ± 20 vs 89 ± 7 μmol/kg LBM/h, $P < 0.05$) and release (59 ± 12 vs 42 ± 14 μmol/kg LBM/h, $P < 0.02$) remained higher in E than in C. Leucine oxidation (43 ± 15 vs.43 ± 12 μmol/kg LBM/h) and leucine balance (+48 ±10 vs +47 ± 12 μmol/kg LBM/h) were the same	WB

AA, amino acid; BMI, body mass index; CRP, C-reactive protein; C, Control Group; DHA, docosahexaenoic acid; EAA, essential amino acid; EPA, eicosapentaenoic acid; E, Experimental Group; FSR, fractional synthesis rate; IL, interleukin; IQR, interquartile range; IV, intravenous; LBM, lean body mass; MPS, muscle protein synthesis; NF-κB, nuclear factor kappaB; NSCLC, non-small cell lung cancer; ONS, oral nutrition supplementation; PHE, phenylalanine; PB, protein breakdown; PS, protein synthesis; TNF, tumor necrosis factor; TYR, tyrosine; WB, whole body.

Potential nutrients for future research

The next section describes other nutrients that could have anabolic effects in cancer. The basic chemical properties and mechanism of action of the nutrients are summarized in Table 2.

Branched-chain amino acids

Branched-chain amino acids (BCAAs) are a group of EAA with a similar lateral radical chain. They are transaminated in skeletal muscle during exercise, generating acetyl-coenzymeA (CoA) to the Krebs cycle and assisting with muscle recovery from exercise. BCAAs also activate the mTOR pathway when glutamine is lacking (e.g., in cancer), and thus reduce protein breakdown and stimulate protein synthesis in cancer [26]. There are three BCAAs: leucine, isoleucine, and valine. Leucine has been studied most extensively regarding its effects on muscle protein synthesis via initiation of signal-transduction pathways [27,28]. Leucine is also a source of HMB.

In mouse cancer cachexia models, a leucine-enriched oral diet resulted in greater maintenance of lean muscle mass than a standard diet [29,30]. Some human studies demonstrated beneficial effects of administration of total parenteral nutrition supplemented with BCAA on muscle protein metabolism by inhibiting protein breakdown and promoting protein synthesis and leucine balance [31,32].

One double-blinded randomized controlled trial (RCT) by Cangiano et al. applied oral BCAA and placebo mixtures for 7 d in patients with resectable cancers. Their study showed marked improvements in metabolic parameters (decreased free tryptophan/large neutral amino acid ratio decreased in BCAA group), reduced incidence of anorexia, and increased energy intake. Effects on protein metabolism were not assessed [33].

Therefore, leucine and a mixture of BCAA administered orally or by parenteral nutrition demonstrated beneficial effects on protein synthesis and other cachexia parameters (e.g., anorexia, dietary intake) in a small number of animal and human studies. More research is needed to test short- and long-term effects of BCAA on muscle protein synthesis in individuals with cancer.

HMB

HMB is a metabolite of leucine and has an inhibitory effect on protein breakdown via a number of mechanisms [34,35]. HMB suppresses the ubiquitin-proteasome proteolytic pathway, upregulates protein synthesis via the mTOR pathway, and stabilizes cell membranes via the rate-limiting enzyme to cholesterol synthesis HMG−CoA reductase [34]. It also can decrease cell apoptosis, thus improving cell survival; and increase proliferation and differentiation of muscle stem cells, via the MAPK/ERK and PI3 K/Akt pathways [35]. HMB directly enhances muscle protein synthesis and mitochondrial dynamics in skeletal muscle via several metabolic pathways [36,37]. A few studies have shown increases in lean mass, muscle strength, and physical performance after adding HMB to a high-protein ONS in geriatric [15,38,39], perioperative, and rehabilitation settings [35]. No solid conclusions can be drawn from these heterogeneous studies, and the effects of HMB on muscle maintenance or buildup and clinical outcomes needs to be confirmed.

In humans with cancer, three studies have investigated the effect of HMB, supplemented as part of an amino acid mixture. One study applied a daily dose of 3 g HMB, 14 g arginine, and14 g glutamine versus an isonitrogenous mix of non-essential amino acids for 24 wk in an RCT including 32 weight-losing patients with cancer. The intervention group gained 1.12 kg of fat-free mass (FFM), the control group lost 1.34 kg of weight on average, and the intervention group maintained their FFM at 24 wk (intervention: +2.27 kg versus controls: +0.27 kg) [40]. A large RCT was conducted with 472 weight-losing individuals with advanced cancer, applying HMB, arginine, and glutamine for 8 wk. The intervention group showed a trend toward higher lean mass; however, statistical significance was not reached. Only 37% of participants completed the study, which could have affected the results [41]. Another study applied perioperative nutritional support with HMB, arginine, and glutamine (1.2 g HMB, 7 g L-Arg, and 7 g L-Gln) or placebo (isocaloric juice) in 60 subjects undergoing surgery for abdominal malignancies. Supplements were provided once daily for 3 d preoperatively and once daily for 7 d postoperatively; the primary outcome of the study was incidence of wound complications. No significant differences were found in body composition or

Table 2
Basic chemical properties and mechanism of action of nutrients with potential beneficial effects on muscle protein synthesis in cancer

Agent	Basic chemical properties
Branched-chain amino acids	• Essential amino acids with a similar lateral radical chain (leucine, isoleucine, valine) • Transaminated in skeletal muscle during exercise and assisting with muscle recovery • Activate the mTOR pathway when glutamine is lacking (e.g., in cancer)
β-hydroxy-β-methylbutyrate	• α-amino acid • Used in biosynthesis of proteins • Conditionally essential in states where tissue is being built or repaired (illness, wound healing)
Creatine	• Synthesized in the body from glutamate and ammonia • Organic compound • Facilitates recycling of ATP • Synthesis in liver and kidneys from glycine and arginine • Tissues with high energy demands (brain and skeletal muscle) • Creatine kinase in brain/muscles: resynthesizes ATP from ADP to meet increased energy demands
Carnitine	• Trimethylated amino acid (roughly similar in structure to choline) • Plays a central role in the metabolism of fatty acids • Antioxidant and anti-inflammatory properties • Cancer increases the risk of carnitine deficiency
Arginine	• Conditionally essential amino acid (the body cannot produce in sufficient amounts during stress) • Availability depends on dietary intake and the de novo synthesis from citrulline • Dietary arginine and citrulline stimulate muscle protein synthesis (citrulline is more effective per gram than arginine)
Glutamine	• Conditionally essential amino acid • Glutamine is converted to citrulline in the gut, and in the kidneys metabolized to arginine + NO • Protects normal tissues from chemo-related injury, and sensitizes tumor cells to chemotherapy and radiation

ADP, adenosine diphosphate; ATP, adenosine triphosphate; mTOR, mammalian target of rapamycin; NO, nitric oxide.

handgrip strength (HGS). Serum growth hormone (GH) levels were significantly higher for patients whose total intake was >80% of planned volume in the HMB, arginine, and glutamine group [42].

With regard to HMB supplementation in humans, there are insufficient studies to draw any conclusions on its effects on protein metabolism in cancer.

Creatine

Creatine (*N*-aminoiminomethyl-*N*-methylglycine) is produced in the body from glycine and arginine, requiring methionine to catalyze the transformation to creatine. It plays an essential role in rapid energy provision during skeletal muscle contraction [43] and is endogenously synthesized or ingested from the diet. It has been shown to impair energy metabolism and reduce tumor growth in animals. A 70-kg person has a creatine pool of 120 g and produces 2 g/d from dietary and endogenous sources. Supplementation of creatine temporarily reduces the normal production in the body and increases creatine phosphate stores. Creatine supplementation in athletes improved exercise performance and muscle mass [44].

In cancer, one study showed that 8 wk of creatine supplementation in (non-cachectic) patients with colorectal cancer did not exert any changes on QoL or in nutritional parameters, but did show improvements in HGS and bioelectrical characteristics of the cell membrane, such as capacitance and phase angle. These parameters were correlated with longer survival [45].

In a double-blind placebo-controlled trial by Jatoi et al., 263 patients with incurable malignancies and anorexia/cachexia symptoms were assigned creatine for 7 d (20 g/d load × 5 d followed by 2 g/d orally) versus identical placebo. The results showed that only three individuals gained ≥10% of their baseline weight by 1 mo: two creatine-treated and the other placebo-exposed ($P = 1.00$), and there were no differences between groups for appetite, QoL, activities of daily living, HGS, or body composition [46]. However, a 10% weight gain is not achievable within such a short time frame, and body composition was assessed by bioimpedance analysis only in subgroups of 20 creatine-treated patients and 15 who were exposed to placebo, and results on body composition were not reported. This might have skewed the results of this study.

With only two studies available with inconclusive effects of creatine, more research on short-term metabolic effects and muscle mass and strength in patients with cancer is required.

Carnitine

Carnitine is a trimethylated amino acid roughly similar in structure to choline. It is derived mainly from meat and dairy dietary sources, plays a central role in the metabolism of fatty acids, and has antioxidant and anti-inflammatory properties. In skeletal muscle and heart muscles, carnitine regulates the mitochondrial ratio of free CoA to acyl-CoA, which is required for fatty acid oxidation. Individuals with cancer, especially those who are underweight or with cachexia, are at risk for and often present with carnitine deficiency [47].

Individuals with cancer often have a decreased caloric intake and increased metabolic requirements, and numerous antineoplastic drugs can interfere with the absorption and synthesis of carnitine [47]. This has led to preliminary studies on L-carnitine supplementation in patients with cancer cachexia. Overall, these studies indicate improved fatigue and QoL, and improvements in nutritional variables of appetite, total body weight, and LBM.

Studies by Kraft et al. [48] and Gramignano et al. [49] showed L-carnitine supplementation resulted in significant improvements in BMI [48], LBM, and appetite [49]. In a study by Mantovani L-carnitine supplementation in combination with a progestational agent, eicosapentaenoic acid, and thalidomide had a positive effect on LBM, fatigue, and appetite. However L-carnitine supplementation alone did not have the same positive effect [50].

Gramignano et al.'s study of 12 individuals with advanced cancer confirmed the significant improvement of fatigue and QoLwith L-carnitine supplementation (6 g/d). Similarly Mantovani's large phase III study demonstrated interim results of significant improvements in fatigue when 4 g/d L-carnitine was supplemented [50]. Despite this promising preliminary result, L-carnitine did not affect any primary endpoints such as fatigue or LBM and appetite in cancer. It did, however, affect secondary outcomes such as performance status and inflammation-based prognostic scores [50].

There is evidence that L-carnitine is able to reduce chronic inflammation and oxidative stress in cancer. Several animal studies have shown the anti-inflammatory effects of L-carnitine supplementation [51,52]. Gramignano et al. found that levels of reactive oxygen species decreased, and glutathione peroxidase increased with L-carnitine supplementation in individuals with advanced cancer, but not significantly. Proinflammatory cytokines also did not change significantly [49].

These studies highlight that L-carnitine is an interesting potential agent in the treatment of cancer cachexia; however, the efficacy of such supplementation to improve cachexia symptoms requires further investigation. These studies shed light on some of the longer-term effects in individuals with cancer; however, short-term metabolic effects of L-carnitine supplementation is yet to be investigated in human studies.

Glutamine and arginine

Glutamine and arginine are conditionally EAAs, which means that the body can produce them, but not in sufficient amounts during stress. Glutamine is converted to citrulline in the gastrointestinal (GI) tract, and in the kidneys it is metabolized to arginine plus nitric oxide [53]. The availability of arginine depends on dietary intake and the de novo synthesis from citrulline. There are indications that dietary arginine and citrulline stimulate muscle protein synthesis. Citrulline is more effective per gram than arginine. As citrulline gets converted into arginine, it could be effective in stimulating muscle protein synthesis [53].

In cancer, there has been a lot of interest in the effects of glutamine on GI toxicity, for instance during radiation or chemotherapy. Emerging evidence suggests that supplementation of oral glutamine decreases the incidence and/or severity of chemotherapy-associated mucositis, diarrhea, neuropathy, veno-occlusive disease, and cardiotoxicity. It is suggested that glutamine protects normal tissues from chemotherapy-related injury, and sensitizes tumor cells to chemotherapy and radiation [54]. A retrospective study by Gul et al. looked at the effects of oral glutamine powder (10 g three times daily) on acute radiation-induced esophagitis and weight loss and survival in patients with NSCLC. During a median follow-up of 13 mo, there was a lower prevalence of severe esophagitis and less weight loss in the supplemented group [55,56]. These results need to be confirmed by well-designed prospective studies.

Arginine activates the mTOR signaling pathway in muscle tissue and in this way enhances protein synthesis and possibly inhibiting proteolysis [57]. In healthy individuals, arginine administration enhanced exercise endurance and muscle force [57]. Dietary supplementation of arginine in cancer has mostly been studied in perioperative settings as part of immunonutrition. There is some evidence that immunonutrition reduces the surgery-induced immune suppression, postoperative complications and infections, and hospital length of stay [58].

Despite the application of glutamine and arginine in human research, there are no studies on acute effects of glutamine and arginine on protein metabolism in individuals with cancer.

Conclusion

Amino acids from protein are known to be the building blocks of muscle mass and are required to achieve muscle maintenance in individuals with cancer. This review summarized the existing metabolic studies on effects of oral administration of amino acids or their metabolites. The studies showed that individuals with cancer are able to achieve protein anabolism in response to a high-protein oral meal or supplement. This occurred in individuals with early and more advanced stages of cancer, and in those with inflammatory and critical weight loss, as well as in patients with a stable weight. Mixtures high in EAAs were more effective than traditional amino acid mixtures. BCAAs have beneficial short-term effects on protein metabolism, but more research is needed. This also applies to other nutrients that have been claimed to be anabolic, such as HMB, creatine, and L-carnitine.

The identified studies were small and differed with regard to cancer types, disease stage, inflammatory state, levels of involuntary weight loss, and type of oral intervention. We advocate larger acute as well as long-term metabolic studies in common types of cancer. Additionally, more research is needed on the metabolic effects of other nutrients that are claimed to have positive effects on muscle buildup in individuals with cancer, such as vitamin D and ω-3 PUFAs from fish oil. As there could be a synergistic effect of combination supplements, future research should also focus on the effects of a multicomponent approach combining a number of effective nutrients.

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