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The nutritional/metabolic response in older cancer patients

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Keywords

anabolic response; skeletal muscle; older cancer patient; amino acid

The “sugar feeds cancer” concept is well known among physicians, scientists and cancer patients alike. It denotes that glucose plays a key role in tumour metabolism by promoting cancer cell growth and division. Cancer cells utilize glucose at a much higher rate than non-cancer cells, but this should not translate in a clinical recommendation to cancer patients to avoid eating glucose or simple sugars (carbohydrates). Moreover this would prove challenging for patients because carbohydrates constitute the largest proportion of the US Recommended Daily Intake (RDI) among the three macronutrients (carbohydrates, fat and protein). In healthy persons, it is generally accepted that 20–35% of the total daily caloric intake should come from fat, with approximately 50–60% of intake coming from carbohydrates. However, it is hotly debated among scientists as to the appropriate RDI for protein, though the current US RDI remains 0.8 g/kg/day. While the debate rages for the appropriate RDI for protein in healthy adults, little attention has been directed to the nutritional needs of the cancer patient, regardless of age. Plasma levels of all the essential amino acids (except tryptophan and in some cases threonine) are lower in cancer patients [1–9] which suggests inadequate nutritional intake. Interestingly, the A.S.P.E.N Clinical guidelines [10] do not appear to mention amino acids, whereas the ESPEN Guidelines [11] on parenteral nutrition in non-surgical oncology patients recommends a minimum protein supply of 1g/kgBW/day, and a target supply of 1–1.2 g/kgBW/day. Regardless, the rationale for enhanced intake of protein and amino acid sources in cancer patients is simple: to provide an anabolic stimulus to skeletal muscle during a time when it is susceptible to an advanced rate of breakdown due to cancer- and tumour-related factors. Therefore, the major focus of this paper is protein and amino acid support in older cancer patients.

Amino acids and loss of muscle mass in older cancer patients

Involuntary weight loss is common in older individuals and is often associated with susceptibility to infection and reduced quality of life and survival. Besides starvation (lower dietary intake), a large component of this involuntary weight loss in older persons is a loss in

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fat free mass (skeletal muscle). This age-related decline in muscle mass is called sarcopenia. Similarly, older cancer patients often suffer from cachexia, a wasting of protein and energy stores likely due to a number of cancer- and non-cancer-related factors (tumour-derived factors, inflammation, inactivity, inadequate nutritional support). Worldwide, it is estimated that approximately 2 million people will die annually due to the consequences of cancer-related cachexia. Cachexia is present in approximately 50% of all cancer patients, and is characterized by a severe loss of body weight, with losses of skeletal muscle proteins approaching 75% when the patient has lost 30% of body weight. Muscle wasting is by far the most important phenotypic feature of cancer cachexia, although little success has been achieved in reversing or preventing this catabolic process. New targeted nutritional therapies aimed at improving lean body mass via regulation of both the synthetic and proteolytic pathways of muscle protein balance are clearly needed.

The combination of age-related muscle loss (sarcopenia) and the diagnosis of cancer (and the onset of cachexia) is likely a metabolic challenge that older skeletal muscle is not prepared to handle. The resulting metabolic abnormalities can include increased glucose turnover, increased lipolysis, dysregulated hormone housekeeping (e.g. hypogonadism), increased insulin resistance, decreased muscle protein net balance, elevated cytokines, and elevated acute phase proteins synthesis [12]. This can lead to a complex metabolic syndrome in the often nutritionally compromised older person, greatly impacting cancer therapy and quality of life. Thus, it is important for physicians and scientists to offer targeted nutritional support so that the processes of involuntary weight loss can be halted to decrease the risk of complications and death during the course of cancer treatment.

Metabolic response in older cancer patients and that of healthy older controls

An important first question for physicians and scientists is: Is the skeletal muscle of older cancer patients anabolically responsive to protein or amino acid support, or is elevated muscle catabolism responsible for sustaining cancer cachexia? Normal dietary intake in the form of mixed medical food based on casein protein alone has been shown to be minimally anabolic to the skeletal muscle of cancer patients [13]. Further, whole body protein turnover in cancer patients appears to be elevated compared to healthy controls [14–16], however, the rate of muscle protein synthesis has been reported to be reduced in older patients (~61 years) with established cachexia [17]. Regardless of which side of the metabolic equation is driving muscle catabolism, even this limited evidence suggests that more research is needed to define the proper nutritional support for the older cancer patient.

There is much to learn from the literature from scientists studying muscle loss with aging that can be applied to cancer. Maintenance of muscle mass in aging or cancer requires that the net balance of muscle protein synthesis and breakdown should remain positive. In the literature on aging and sarcopenia, the approach has been to focus on stimulating the muscle protein synthesis side of the metabolic equation, as muscle protein breakdown does not appear to be a major determinant in muscle loss with aging. In cancer or aging, this can be done by adding amino acids such as leucine, the principal nutrient responsible for the stimulation of muscle protein synthesis [18], to high protein supplements [19–21], or to

balanced meals with a lean protein source [22]. Although it is known that age-related differences exist in the time course of the anabolic response to nutritional support, ingestion of amino acids acutely [23–25] and chronically [26] stimulates muscle protein anabolism [27] in older healthy adults.

Using stable isotopic methodologies and the tracer phenylalanine, Dillon et al. [28] showed that 40 g of mixed AAs given in small boluses to avoid GI symptoms acutely stimulates muscle protein synthesis in a mix of younger and older ovarian cancer patients (Figure 1). Interestingly, the authors note that the magnitude of the protein synthetic response to the amino acid provision was greatly diminished in the older cancer patients compared to that of their younger cancer counterparts. Overall, the ovarian cancer patients showed similar leg blood flow, muscle fractional synthesis rate and arterial phenylalanine enrichments as in healthy older subjects [28], although the arterial phenylalanine concentrations were lower in the ovarian cancer patients compared to healthy older controls in both basal and amino acid periods. This suggests that a part of these exogenous amino acids were used for other metabolic purposes, such as acute phase protein synthesis. Further, the increase in muscle protein synthesis from basal to essential amino acids was smaller in the ovarian cancer patients [28] compared to the healthy older controls [27] (Figure 1). Finally, Figure 1 shows that Deutz et al. [13] found that muscle anabolism is possible in response to a medical food in older (~67 years) non-small cell lung cancer and colon cancer patients.

While skeletal muscle anabolism in response to an amino acid provision in older healthy persons can be robust, it is also known that with aging comes a degree of skeletal muscle anabolic resistance [29–31] to amino acids, which one could also assume might be the case in the muscle of older cancer patients.

Thus, we predict from the literature on aging and sarcopenia and from the findings of Dillon et al. [28] that the metabolic response in older cancer patients is slower and blunted compared to older healthy people or younger cancer patients, and Figure 2 graphically depicts our estimation.

In conclusion, this brief review suggests that the skeletal muscle of older cancer patients is acutely anabolic to the provision of amino acids, albeit to a smaller extent than healthy older controls. A diminished anabolic response in cancer patients should not be construed as a recommendation against supplementing cancer patients with amino acid support, rather, it should serve as a lesson from the literature on aging and skeletal muscle that we as scientists need to work on finding ways in which to make the skeletal muscle of cancer patients more sensitive to the anabolism of amino acids. Considering that the muscle of cancer patients is metabolically challenged with the toxicity of chemotherapy, inflammation, and tumor-factors etc., it is likely that greater than 0.8 g/kg/day of protein is required in addition to other non-nutritional pharmacologic approaches. Finally, future studies should investigate whether the acute effects of amino acids on muscle protein anabolism can be sustained over a longer period of time in the presence of cancer cachexia. This review demonstrates that a number of lingering questions remain: 1) What role does muscle breakdown play in cachexia?, 2) What would be the most efficacious dose of amino acids in older cancer patients?, 3) How does a mixed meal (carbohydrate + protein + fat) alter the muscle protein

synthesis response in older cancer patients? Further investigation with answers to these questions will give us the necessary information to provide cancer patients appropriate nutritional support to maintain muscle mass and muscle health during cancer treatment.

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KEY POINTS

- Older cancer patients' skeletal muscles' anabolic response to amino acids is blunted
- The acute response is smaller than in young cancer patients and healthy old adults
- Despite reduced sensitivity, the skeletal muscle remains responsive to amino acids
- We suggest chronic amino acid supplementation in older cancer patients
- It remains untested whether this will benefit maintenance of skeletal muscle mass

Figure 1.

The muscle protein fractional synthesis rate (FSR) in young healthy (YH) subjects, old healthy (OH) subjects, young cancer (YC) and old cancer patients (OC) in the fasted state (basal) and after ingestion of essential amino acids (EAA).

Figure 2.

The net phenylalanine balance (Phe NB) of muscle protein in the post-absorptive condition and after ingestion of essential amino acids (EAA) in healthy young, healthy old, and in younger and older cancer patients.