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High-Protein Supplementation during cancer therapy – strengthening of the evidence-base to support its safety and clinical benefits.

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With sarcopenia and low muscle attenuation emerging as key predictors of poor outcomes in cancer(1), maintaining muscle mass, quality and strength over the course of oncological treatment, has become an increasingly important part of the battle that many patients with cancer must face. It is now well established that muscle loss is linked with impaired physical function, reductions in quality of life, poorer tolerance to chemotherapy, increased respiratory failure and surgical complications, and decreased survival(1–7).

Cancer therapies can exacerbate weight and muscle loss. For example, the nutritionally relevant symptoms associated with chemotherapy, such as nausea, vomiting, diarrhoea, xerostomia, and dysgeusia, can lead to reduced food intake(8,9). Similarly, radiation therapy can induce anorexia, fatigue, mucositis, xerostomia, dysphagia and radiation enteritis, impeding a patient's ability to consume and absorb sufficient nutrients(10). The physiological effects of cancer surgery are an additional contributing factor to nutritional deterioration for patients, through the combined effects of reduced oral intake, malabsorption, and nutrient losses(11,12).

The metabolic changes associated with cancer, predominantly a pro-inflammatory state, accelerates muscle catabolism and reduces muscle protein synthesis(4,13). This altered balance of reduced oral intake and/or absorption, coupled with increased catabolism, increases the protein requirements of patients with cancer, underscoring the potential benefits of high-protein supplementation as a viable strategy to address this catabolic condition. To-date however, there are gaps in the evidence-base regarding the optimal timing and dose of protein supplements and their clinical efficacy.

In this issue of *The American Journal of Clinical Nutrition*, a systematic review and meta-analysis of 34 unique studies conducted by Orsso et al.(14), investigates the evidence of high-protein supplementation (at doses of 10-14.9 g protein/serving or ≥ 15 g protein/serving or providing a total daily protein intake of ≥40g) on various patient-reported and clinical outcomes during cancer therapy. The overall findings of this review support the safety of high-protein supplementation and found that its use can lead to beneficial outcomes for patients undergoing oncological treatment including mitigation of body weight decline, improved handgrip strength and lower rates of hospitalization(14). While the review did not find direct benefits of high protein supplementation on cancer patients' health-related quality of life, no serious adverse effects were reported. These findings are the first time a meta-analysis has shown that high-protein supplementation has meaningful clinical effects, and also helps to alleviate the concerns among some professionals and patients about the misconception that "nutrition feeds the tumour".

Weight loss prior to cancer treatment is a common phenomenon and is linked to poorer outcomes. Even a modest weight loss of 2.4%, can adversely impact survival, independent of the cancer site, stage, or performance status(15). A subgroup meta-analysis completed as part of this review revealed that high protein-supplementation had a positive effect on the body weight of patients with prior weight loss(14). Furthermore, this systematic review found that 85% of included studies showed that high protein-supplementation had a beneficial impact on muscle mass when compared to controls(14). Steps in the right direction, however, consistent with our current scientific understanding(16), the increased systemic inflammation experienced by patients during treatment remains a challenge, and was observed to inhibit gains in muscle mass in 60% of the studies reviewed by Orsso et al.(14).

Given the high risk of bias observed across the included studies, the authors acknowledge that their conclusions should be interpreted with some reservation. They recognize the importance of building on the findings of this review with more robust clinical nutrition trials which include clear methodological descriptions of the assessment techniques employed(14).

The *ESPEN Guidelines on Nutrition in Cancer Patients*(16) recommend that protein intake in adults should exceed 1 g/kg/day and, ideally up to 1.5 g/kg/day. These guidelines characterise the level of evidence to support this recommendation as 'moderate' in quality and call for future research to focus on examining the effect of both a greater protein supply (1–2 g/kg/day) and the composition of protein/amino acids on clinical outcomes(16). Orsso et al. provide useful insight into these research gaps, by aiming to investigate them as part of their analysis.

Adding to our understanding, Orsso et al.'s subgroup meta-analyses revealed that specific types of high protein supplementation, such as high protein oral nutritional supplements (ONS), as well as supplements enriched with omega-3 fatty acids, yielded a significant positive effect on body weight(14). In relation in muscle mass, supplements containing branched-chain amino acids (BCAA), and those enriched with hydroxymethylbutyrate (HMB) and omega-3 fatty acids, were found to have a beneficial effect(14).

Following Orsso et al.'s analyses, a positive effect on body weight was observed with high protein supplements containing 10-14.9g or ≥15 g of protein per serving(14). While the optimal dose of protein required to stimulate muscle protein synthesis warrants further

investigation, the authors estimate from their analyses that the needs of patients with cancer is likely greater than the 1g/kg/day recommendation(14).

According to Orsso et al.'s findings, high-protein supplementation may help reduce hospital admission rates for oncological patients undergoing treatment. If a nutritional intervention such as high-protein supplementation during cancer therapy were able to lower the rates of hospital admissions for this patient cohort, this would prove advantageous to both patients and healthcare systems, by potentially leading to cost savings(17,18).

To achieve the best outcomes for patients with cancer, healthcare professionals should prioritize early nutritional screening. The early identification of weight loss and abnormal body composition phenotypes (i.e. reduced muscle mass, low muscle attenuation by CT scans) will allow for the initiation of timely and continued nutritional care, in parallel with medical cancer treatment. This review contributes significantly to the informed decision-making in nutritional oncology care and should serve as a key resource for healthcare professionals and nutrition guidelines. It calls for the incorporation of its findings into clinical practice by considering high-protein supplementation, especially for patients experiencing weight loss(14).

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