Saudi Journal of Medicine and Public Health

https://saudijmph.com/index.php/pub

https://doi.org/10.64483/jmph-120

The Interface of Nutrition and Immunity: An in-depth look at nutritional interventions for the oncology patient receiving immunotherapy

Saad Laiban B Al Rowaili[(1)], Ali Saeed Al Alshiak[(1)], Abdullah Esse Al khamis[(1)], Adel Abdullah Al Shggag[(1)], Eman Ghannam Alotaibi[(1)], Maha Shreedah Alenazi[(1)], Dalal Mohmmed Al-Dosiry[(1)], Azhar Ali Albdiawy[(1)], Mohammed Ibrahim A Alrajal[(1)], Abdullatif Abdulrhman Alsaeed [(1)], Fatimah Saeed Alyagoub[(2)], Dhaha Hassan Al-Saffar[(3)]

[(1)]Eradah (Al Amal) Mental Health Complex, Dammam, Nutritionist, Ministry of Health, Saudi Arabia
[(2)]Maternity and Children Hospital, Nursing technician, Ministry of Health, Saudi Arabia
[(3)]Al-Majidiyah Health Center in Qatif, Nursing technician, Ministry of Health, Saudi Arabia

Abstract

Background: Immunotherapy, as immune checkpoint inhibitors (ICIs), has revolutionized oncology by taking advantage of the patient's native immune system to combat cancer. Although responses are heterogeneous, immune-related adverse events (irAEs) can limit treatment benefit and decrease quality of life. A growing appreciation is arising that host factors, including nutritional status and diet, play an important role in determining the immune response and tumor microenvironment.

Aim: The objective of this review is to provide an overview of the current evidence relating to nutritional strategies in cancer immunotherapy patients. It considers the ruinous role of malnutrition (cachexia) in clinical outcomes, reviews the mechanisms by which particular dietary components influence anti-tumor immunity and treatment side effects, and provides a model for the practical assessment and management of nutritional deficits.

Methods: A systematic review of the literature was conducted through the utilization of leading scientific databases (e.g., PubMed, Scopus, Web of Science) to identify preclinical, clinical, and review articles published up to 2024. Search terms were permutations of "immunotherapy," "immune checkpoint inhibitors," "nutrition," "diet," "cachexia," "microbiome," and "immune-related adverse events." The evidence was synthesized to provide a narrative review of the existing literature.

Results: There is evidence that indicates that sarcopenia and malnutrition have a close correlation with poorer efficacy of ICI and increased toxicity. Individual nutritional interventions are promising for modulating outcomes: adequate consumption of good-quality protein is crucial for the avoidance of muscle wasting and immune function maintenance; dietary fiber and omega-3 fatty acids exert anti-inflammatory effects and preserve a healthy gut microbiome; the Mediterranean diet and vegetarian dietary patterns are related to improved survival; and micronutrients like Vitamin D have a role in immune regulation. The gut microbiome is identified as a mediator between diet and immunotherapy response.

Conclusion: An active, individualized nutrition approach, emphasizing a whole-food, plant-based diet, adequate protein, specific micronutrients, and gut microbiome support, is very promising as an adjunctive strategy to enhance the efficacy and tolerability of immunotherapy. Further robust, prospective clinical trials are needed to solidify specific recommendations and integrate nutritional therapy into the standard armamentarium of immuno-oncology treatment.

Keywords: Immunotherapy, Clinical Nutrition, Cancer Cachexia, Gut Microbiome, Immune-Related Adverse Events.

1. Introduction

The landscape of cancer therapy has been drastically transformed by immunotherapy, a therapeutic approach to utilizes the immune system of the host to recognize and kill cancer cells (Weenink et al., 2020). Among the most powerful immunotherapeutic approaches are immune checkpoint inhibitors (ICIs), which regulate regulatory pathways such as PD-1, PD-L1, and CTLA-4 to regain T-cell-mediated anti-tumor immunity (Ribas & Wolchok, 2018). Although such remarkable and durable responses have been reported in a percentage of patients across several malignancies, there are still significant barriers remaining. Primary and acquired resistance are common, and the majority of patients experience immune-related adverse events (irAEs), which can affect nearly any organ system and range from mild to life-threatening (Postow et al., 2015).

This diversity in response to treatment and toxicity has led to active investigation into predictive biomarkers and host factors that are modifiable and maximize the therapeutic index of ICIs. Nutrition, here, has emerged as a key and controllable component of the internal host environment (Munteanu & Schwartz, 2022). The metabolic and inflammatory state of the patient, gut microbiota profile, and availability of specific nutrients are now recognized to profoundly affect immune cell function,

*Corresponding author e-mail: salrowaili@moh.gov.sa (Saad Laiban B Al Rowaili).
Receive Date: 18 September 2025, Revise Date: 29 September 2025, Accept Date: 13 October 2025

systemic inflammation, and tumor microenvironment (TME) (He et al., 2021).

Cachexia in cancer, a multifactorial etiology syndrome of ongoing loss of skeletal muscle (with or without loss of fat mass), is a powerful negative prognostic factor for all cancers and increasingly is being associated with poor responses to immunotherapy (Peterson & Mozer, 2017). Conversely, initial preclinical and clinical data suggest that specific food constituents and dietary habits can modulate a more favorable immune response. For instance, the gut microbiota has emerged as a determinant of the efficacy of ICI, with specific commensal bacteria enhancing anti-tumor immunity (Gopalakrishnan et al., 2018; Routy et al., 2018). Diet is similarly a critical controller of the structure and function of gut microbiota and, therefore, renders nutritional consumption a causative agent in treatment outcome (Lee et al., 2021).

This review aims to integrate the evidence completely on nutritional strategies for patients undergoing immunotherapy. We will begin with the impact of malnutrition and cachexia on outcomes. We will then discuss the evidence for individual macronutrients, micronutrients, and diets, their potential mechanisms of action, and irAEs and nutrition-impact symptom management from a dietetic perspective. Finally, we will provide an applied focus on nutritional screening and treatment in this patient population, with attention to knowledge deficits and research directions.

The Detrimental Effects of Malnutrition and Cachexia

Malnutrition is very prevalent in oncology patients, with the most severe form being cancer cachexia. Cachexia is not starvation; it is a hypermetabolic, catabolic illness involving a complex interplay of tumor-secreted factors, systemic inflammation, and metabolic dysregulation (Argilés et al., 2014). The defining features of cachexia are anorexia, involuntary weight loss, and the specific loss of skeletal muscle mass, which is a primary marker of poor outcomes.

The cachexia effect on immunotherapy response is negative and multi-level. Skeletal muscle is not merely a tissue with a structural function; it is an immunocompetent organ. Myocytes produce and release cytokines and myokines that can control systemic immunity (Penna et al., 2019). Muscular wasting is associated with a state of chronic, low-grade inflammation, which is demonstrated by higher concentrations of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. This inflammatory microenvironment can induce T-cell exhaustion, increase the frequency of immunosuppressive populations like myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs), and promote a TME that is not supportive of effective anti-tumor immunity (Flint et al., 2017).

Clinically, various studies have shown a strong correlation between low muscle mass (sarcopenia), as determined by computed tomography (CT) scans, and adverse outcomes with ICI treatment. For example, in NSCLC and melanoma patients who receive ICIs, independent associations of sarcopenia with reduced OS and PFS and increased severe irAEs have been reported (Shiroyama et al., 2019; Munteanu & Schwartz, 2022). This suggests that the patient's initial "nutritional phenotype" is a main predictor of the patient's tolerance to and response to treatment. Therefore, prevention and treatment of malnutrition and wasting of muscles is the initial and most fundamental nutritional goal in any patient undergoing immunotherapy. This requires organized screening and evaluation, which shall be discussed in a later section.

Macronutrients: Propelling the Immune Effort

Protein: The Structural and Functional Substrate of Immunity

Appropriate consumption of protein is an undisputable cornerstone of nutritional management in patients undergoing immunotherapy. The entire immune machinery is inherently proteinaceous; from the structural components of immune cells to the signaling molecules like cytokines and chemokines, and the complement proteins and antibodies that perform immune functions, all require an ever-present and adequate supply of amino acids. The mechanism of action of immune checkpoint inhibitors (ICIs) itself is very protein-synthesis-intensive since it exploits the successful clonal growth and proliferation of antigen-specific T-cells, a process involving vast biosynthetic capacities (Bourke et al., 2023). When protein-calorie malnutrition occurs, it unleashes a cascade of immunosuppression that begins with the atrophy of primary and secondary lymphoid tissues and ultimately leads to decreasing T-cell number and function, thereby effectively compromising the therapeutic potential of ICIs.

The protein requirements of oncology patients are incredibly high compared to other patients, and this is a critical consideration given the extreme incidence of cancer cachexia. Current international guidelines, for example, from ESPEN, are 1.2 to 2.0 grams of protein per kilogram body weight daily to counteract muscle catabolism and support immune reconstitution (Muscaritoli et al., 2021). Quantitative targets are insufficient; the qualitative properties of the protein are also essential. High-biological-value proteins yielding all the indispensable amino acids in suitable ratios for human physiology should take precedence. These great sources include lean poultry, fish, eggs, dairy, legumes, and soy. Among them, branched-chain amino acid leucine has been reported as an essential nutrient signal that serves as a key molecular stimulus for the initiation of muscle protein synthesis and is particularly valuable for the preservation of lean body

mass (Deutz et al., 2014). Moreover, recent findings suggest that protein timing plays a significant role as a determinant of the maximization of metabolic utilization. Having a constant protein supply distributed across meals during the day, approximately 25-40 grams per meal, appears more effective at causing sustained anabolic occurrences compared to consuming the majority of daily protein as one large meal.

Fats: Immunomodulatory Signaling Molecules

The role of dietary fats in immunotherapy is much more significant than that of a dense source of fuel. Fats are structural components of all cellular membranes, regulating the fluidity of membranes and the activity of trapped receptors. Most importantly, they are precursors to a vast array of potent signaling molecules, so the composition of fat consumed can directly skew the immune system towards a pro-inflammatory or anti-inflammatory type, and thus determine the entire immune landscape (Radzikowska et al., 2019).

The omega-3 polyunsaturated fatty acids (PUFAs) EPA and DHA, abundantly found in oily fish (e.g., salmon, mackerel, sardines) and algal oil, are particularly characterised by their potent anti-inflammatory and pro-resolving activities. The fatty acids are incorporated into cell membranes and employed as substrates in the biosynthesis of SPMs, such as resolvins and protectins. SPMs are not only immunosuppressive but also intervene positively in the resolution of inflammation by preventing neutrophil recruitment, triggering macrophage clearance of cellular waste, and inhibiting inflammatory cytokine production (Torres et al., 2023). This mechanism is particularly important in immunotherapy since it offers an EAA dietary solution to control the inflammatory cascade of immune-related adverse events (irAEs) without actually diminishing the intended anti-tumor effect. Furthermore, preclinical studies provide hopeful evidence that omega-3 PUFAs can reorganize the tumor microenvironment positively, reducing the number of immunosuppressive cells and enhancing T-cell invasion, and thereby potentially synergistically enhance the efficacy of ICIs (Fodil et al., 2022).

In contrast, the typical diet of the Western world is characterized by an overreliance on excessive intake of omega-6 PUFAs, which are derived from food items like corn, soybean, and sunflower oils. While required in moderation, omega-6 PUFAs are metabolized to pro-inflammatory eicosanoids (e.g., prostaglandins, leukotrienes). A condition of chronically high dietary ratio of omega-6 to omega-3 PUFAs, typically more than 10:1 in Western diets, is a condition of chronically maintained low-grade systemic inflammation that is harmful to immune homeostasis. Therefore, a first-line dietary solution is to deliberately reverse the ratio by increasing omega-3 consumption while at the same time reducing omega-6 consumption. In addition, excessive saturated fat consumption, usually from processed and red meats, has been epidemiologically linked with systemic inflammation and, in several studies, with an unfavorable composition of gut microbiota. While the effect of saturated fat is more nuanced and may be dependent on the food matrix, a general and conservative recommendation is to limit its intake in favor of unsaturated fats to create a less inflammatory environment (Lee et al., 2021).

Carbohydrates and Fiber: Metabolic and Microbiome Mediators

Carbohydrates are the prime glycolytic fuel of rapidly dividing immune cells, but their influence on immunity is heavily dependent on chemical structure and origin. The most significant distinction is between processed carbohydrate and dietary fiber. Dietary fibre, and to a greater extent the fermentable and soluble fractions that occur in high concentrations in fruits, vegetables, legumes, and whole grains, are not hydrolysed by enzymes of man but constitute the primary fermentable substrate for the distal gut commensal bacteria. The latter undergo fermentation to produce short-chain fatty acids (SCFAs), mainly acetate, propionate, and butyrate, which exert gigantic and systemic immunomodulatory functions (Koh et al., 2016). SCFAs enhance the integrity of the intestinal epithelial barrier, reducing systemic exposure to microbial products and quenching chronic inflammation. SCFAs directly modulate immune cell function; butyrate, for instance, is a histone deacetylase inhibitor with a gene expression effect in immune cells. This can induce the differentiation and activity of regulatory T-cells, which are crucial for immune tolerance and can also be involved in reducing the severity of off-target irAEs such as colitis (He et al., 2021). Most notably, butyrate has been demonstrated to enhance the metabolic wellness and cytotoxic effector function of CD8+ T-cells, possibly creating a synergistic relationship with ICIs by potentially amplifying the very cell type the treatment aims to unleash (Luu et al., 2019). Subsequently, high-fiber diets preserve a gut microbiome configuration that is inextricably associated with a greater response to ICIs in clinical trials.

Conversely, overconsumption of refined carbohydrates and simple sugars found in sweet beverages, white bread, and processed foods has undesirable consequences. These readily available carbohydrates can stimulate the growth of pro-inflammatory microbial pathobionts, leading to gut dysbiosis. These contribute to increased intestinal permeability, often referred to as "leaky gut," which enables bacterial endotoxins like lipopolysaccharide (LPS) to enter the circulation and trigger systemic inflammation. Besides, chronic high sugar intake can lead to insulin resistance, inducing a metabolic condition that is less favorable for the optimal functioning of T-cells. Generally, this diet pattern induces a pro-inflammatory, dysbiotic, and metabolically dysfunctional state, theoretically less

favorable for eliciting a vigorous and effective immune response against cancer, thus necessitating restriction of such foods in the oncology setting (Spencer et al., 2021).

Micronutrients: Required Cofactors for Immunity

Micronutrients, while required in smaller quantities than macronutrients, are critical cofactors and coenzymes for most enzymatic reactions that regulate immune cell metabolism, proliferation, and effector function. Insufficiency of the key vitamins and minerals may lead to profound dysfunctions of innate and adaptive immunity, making the patient unable to respond to immunotherapy.

Vitamin D has played a central role as an immunomodulator. Its role extends well beyond its classical role in calcium homeostasis, as the vitamin D receptor is found on the majority of immune cells, including T-cells and antigen-presenting cells. Upon activation, vitamin D signaling promotes a more tolerogenic immune phenotype with a bias for the generation of regulatory T-cells and suppression of Th1 and Th17 responses, which may be of special value in modulating the underlying excessive inflammation that characterizes most irAEs (Chandler et al., 2020). Epidemiological evidence consistently reports an association between sufficient serum 25-hydroxyvitamin D status and increased survival in various cancers, including in patients treated with ICIs, and suggests the potential role of vitamin D status as a measurable predictor of outcome (Mondul et al., 2017). Whereas large-scale intervention trials are still required to establish causality, the low risk and cost of screening for and treating vitamin D deficiency make it a promising aspect of supportive care.

Zinc is a trace element that plays a crucial role in the normal development and function of the immune system. Zinc is a cofactor for over 300 enzymes that have roles in the synthesis of DNA, cell division, and signal transduction. Zinc deficiency rapidly leads to thymic atrophy, depletion of T-cells, and impaired cell-mediated immunity, such as lowered cytotoxic T-cell and NK function (Wessels et al., 2020). Selenium, built into antioxidant enzymes like glutathione peroxidases, is important in protecting immune cells from oxidative damage built up during their hypermetabolically activated state. It is also critical for the maximal activation and proliferation of T-cells (Avery & Hoffmann, 2018).

The interaction of iron with immunity in cancer is complicated. Iron is required for the proliferation of lymphocytes and the enzymatic production of reactive oxygen species for microbial killing. But anemia of cancer is common, and tumors have the "iron-addicted" phenotype, sequestering iron for their own growth. The impact of intravenous iron supplementation, particularly on tumor burden and the success of immunotherapy, is a delicate balancing act and area of investigative work, requiring judicious clinical prudence (Mleczko-Sanecka & Silvestri, 2021). The general strategy with micronutrient supplementation is to optimize obtaining them through a diversified whole-food diet. Inadequate, unspecific high-dose supplementation is not recommended except in cases where a diagnosed, specific deficiency exists because pharmacologic amounts may sometimes function paradoxically, e.g., as immunosuppressants or pro-oxidants. Figure 1 presents the nutritional modulation of the immune response in cancer immunotherapy.

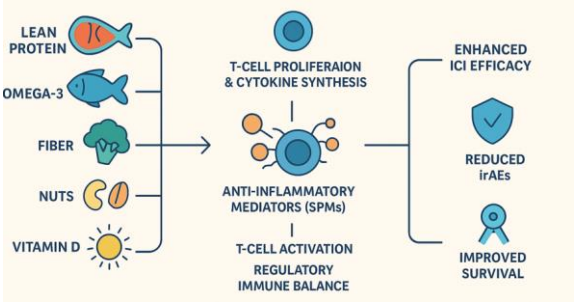

Figure 1. Nutritional Modulation of the Immune Response in Cancer Immunotherapy.

Dietary Patterns: A Synergistic Approach to Nutritional Care

Reductionists focus on individual nutrients, while scientifically valuable, can be burdensome for patient counseling. The concept of dietary patterns constructs a more ecological, true-to-life framework, including the complex synergisms between multiple food components and the overall effect on health. The most extensively studied pattern in this respect is the Mediterranean diet. Characterized by excess intake of fruits, vegetables, whole grains, legumes, nuts, and seeds; olive oil consumption as the major source of fat; moderate fish and poultry intake; and minimal red meat, processed food, and sweet intake, this pattern is always associated with potent anti-inflammatory and antioxidant activity. Its high content of fiber, omega-3 PUFAs, and a diverse array of polyphenols is in itself a prebiotic environment for favoring the growth of a healthy and diversified gut microbiota (Schwingshackl & Hoffmann, 2014). Such a synergistic combination of bioactive compounds is very conducive to immune homeostasis. Notably, initial observational studies in cancer medicine are now connecting these physiological issues to clinical advantages, with evidence amassing that higher adherence to a Mediterranean diet is associated with improved progression-free and overall survival among ICIs-treated patients with advanced cancer (Bolte et al., 2023).

Likewise, plant-based diets, rigorously vegan or vegetarian, or simply "plant-forward," naturally provide a high level of the favorable constituents listed above: dietary fiber, phytonutrients, and key micronutrients. A high fiber level in such diets is a primary driver of a SCFA-producing gut microbiome, which, as demonstrated above, is an excellent predictor of ICI response (Lee et al., 2021).

Conversely, the Western diet, with its high consumption of processed meat, sugary drinks, refined grains, and unhealthful fats, is a clearly established cause of systemic inflammation, oxidative stress, and gut dysbiosis. This trend has been discovered to adversely impact the gut microbiota within mechanisms that are associated with ICI resistance, providing a sound evidence-based rationale for its limitation as a standard recommendation in modern oncology nutrition (Spencer et al., 2021; Table 1).

Table 1. Summary of Key Nutritional Components and Their Proposed Mechanisms in Immunotherapy

Nutritional Component	Proposed Mechanism of Action	Potential Impact on Immunotherapy
High-Quality Protein	Substrate for immune cell proliferation, antibody & cytokine production; prevents sarcopenia by stimulating muscle protein synthesis.	May improve response rates by supporting clonal T-cell expansion and reduce treatment-related toxicity by preserving functional status.
Omega-3 PUFAs	Precursors to specialized pro-resolving mediators (SPMs) that actively resolve inflammation; may modulate the tumor microenvironment.	May reduce severity of inflammatory irAEs (e.g., colitis, hepatitis) and potentially synergize with ICIs to enhance T-cell tumor infiltration.
Dietary Fiber	Fermented by gut microbiota to SCFAs (e.g., butyrate), which enhance gut barrier function, reduce systemic inflammation, and boost CD8+ T-cell function.	Strongly linked to improved ICI response and survival via microbiome modulation; may specifically protect against immunotherapy-induced colitis.
Vitamin D	Binds to vitamin D receptor on immune cells, promoting a tolerogenic phenotype and regulating T-cell differentiation.	Associated with improved survival in observational studies; may help maintain immune balance and reduce the risk of severe irAEs.
Mediterranean Diet	Synergistic combination of fiber, omega-3s, and polyphenols provides anti-inflammatory, antioxidant, and prebiotic effects.	Emerging evidence links higher adherence to significantly improved progression-free and overall survival in patients on ICIs.

The Gut Microbiome: A Master Regulator of Therapeutic Efficacy

The human gut microbiome, comprising trillions of microbes and their combined genetic material, has become a key driver of therapeutic outcome in immuno-oncology. Revolutionary clinical research has unequivocally demonstrated that baseline diversity and composition of gut microbiota can stratify patients based on their likelihood of response to immune checkpoint inhibitors (ICIs). In patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma, responders who showed a clinical response were discovered to have a significantly different and more diverse microbial population than non-responders. Specifically, the enrichment of certain commensals such as the butyrate-producing *Faecalibacterium prausnitzii*, the mucin-degrading *Akkermansia muciniphila*, and Bifidobacterium members has been repeatedly correlated with improved progression-free and overall survival (Gopalakrishnan et al., 2018; Routy et al., 2018).

The underlying mechanisms of such an association are multifaceted and complex, comprising an ongoing dialogue between gut microbiota and the host immune system. One such mechanism that has been suggested is molecular mimicry, in which certain strains of bacteria synthesize peptide antigens structurally similar to tumor neoantigens. Such cross-reactivity can potentially actually "prime" the host T-cell repertoire against cancer cells, creating a pre-existing reservoir of tumor-reactive lymphocytes that are mobilized by ICI therapy. Another, and more fundamental, mechanism is bacterial synthesis of metabolites. Fermentation of dietary fiber by commensal microbes generates short-chain fatty acids (SCFAs) like butyrate, which are significant immunomodulators. Butyrate not only enhances gut barrier integrity, reducing systemic inflammation, but also directly enhances metabolic fitness and CD8+ T-cell cytotoxicity in the tumor microenvironment and thus augments the therapeutic response to ICIs (He et al., 2021). Lastly, the microbiome is also key to the system's education and calibration of the immune response. From lymphoid organogenesis to fine regulation of pro-inflammatory to regulatory T-cell homeostasis, a healthy microbiota is essential to providing a period of immune readiness and homeostasis, a sine qua non for successful anti-tumor immunity.

Critically, diet is the most effective and omnipresent exogenous stimulator for the modulation of the gut community. The above-mentioned nutritional interventions—i.e., the consumption of high levels of varied dietary fiber, high intakes of plant polyphenols, and fermented foods—specifically foster the growth of beneficial taxa associated with beneficial effects. In contrast, the archetypal Western diet rich in processed foods, saturated fats, and refined carbohydrates promotes a culture of dysbiosis with compromised diversity and dominance of pro-inflammatory strains, a culture predictably correlated

with primary resistance to ICIs. The most compelling evidence of the microbiome's dramatic impact, however, is the effectiveness with which fecal microbiota transplantation (FMT) can circumvent resistance. Clinical trials have established the potential for employing the fecal microbiome of responding patients treated with ICIs and transferring it to patients who are refractory and re-sensitizing a subset of patients to treatment with remarkable tumor regressions (Davar et al., 2021). Even though FMT is an invasive medical procedure, it is the final proof-of-concept that building a "favorable" gut community is viable as a treatment modality with diet as the keystone tool for its formation and maintenance.

Nutritional Management of Treatment-Related Symptoms and Toxicities

The efficacy of immunotherapy can be compromised by a variety of side effects that interfere directly with nutritional intake, absorption, and metabolic function. An active and tailored nutritional approach is therefore an integral component of supportive care aimed at guaranteeing quality of life and intensity of treatment dose. Immunotherapy-induced colitis is one of the most frequent and disabling of the immune-related adverse events (irAEs). Its nutritional treatment is biphasic. During the acute inflammatory phase, the primary goals are to reduce bowel frequency, cramping, and inflammation. This can involve a temporary switch to a low-residue diet that excludes fiber and roughage to reduce fecal bulk and mechanical irritation. White bread, white rice, bananas, and applesauce are usually well tolerated. Even a temporary trial of a low-FODMAP diet is beneficial because it does away with poorly absorbed and fermentable carbohydrates that can exacerbate bloating, gas, and diarrhea by increasing osmotic load and gas production in the diseased colon (Tang et al., 2021). Caffeine, alcohol, and fatty or spicy foods, which are dietary irritants, must be avoided at the same time. As inflammation starts resolving with appropriate immunosuppressive treatment and the patient enters a period of recovery, slow and regulated refeeding with fiber is critical. To start with, soluble fibers from sources like oats, psyllium husk, and thoroughly cooked vegetables can help reconstitute normal bowel function and, more importantly, provide essential prebiotic substrates to reconstitute the gut microbiome, which most likely has been disturbed by both the colitis and the restriction.

For the remaining irAEs, nutritional interventions are adjuncts to medical treatment. When there is hepatitis secondary to immunotherapy, nutritional therapy should adhere to standards for liver inflammation and can start with low-fat intake to avoid overloading the inflamed liver metabolically and cholestatically. For pancreatitis, nil-by-mouth can be initially with very slow reintroduction of food under strict medical monitoring. The pervasive signs of anorexia and fatigue associated with cancer require the application of a different strategy for energy conservation and maximization of nutrient density. Methods such as consuming small, frequent meals and snacks every two to three hours, utilizing high-calorie, high-protein oral nutritional supplements or smoothies, and having ready-to-eat foods placed in easy and accessible areas can enable patients to meet their high nutritional requirements with little effort (Berger et al., 2015). First-line treatment of nausea and vomiting is with antiemetics, but dietary modifications may also alleviate the symptoms. Recommending bland, dry foods in small amounts (e.g., crackers, toast, pretzels), ginger foods or tea, cool, clear fluids, and liquids for patients to drink between rather than with meals may quiet the stomach as well as prevent dehydration (Table 2).

Facilitating a Systematic Nutritional Care Protocol in Oncology Practice

To bring therapeutic nutrition's promise to fruition in the form of true clinical benefits, an orderly and systematic approach to care must be integrated into the standard immuno-oncology protocol. It begins with comprehensive screening for nutritional risk at the time of diagnosis and consistently over the course of treatment. Use recommended tools such as oncology-specific Patient-Generated Subjective Global Assessment (PG-SGA) or Malnutrition Screening Tool (MST) on a routine basis to screen individuals at risk in a timely fashion (Muscaritoli et al., 2021).

Screened patients found at risk subsequently need a full assessment by an oncology-trained registered dietitian. This approach goes beyond simple weight assessment and includes an extensive dietary history, nutritional-impact symptom assessment, anthropometric measures, and, where feasible, body composition. The frequent use of computed tomography (CT) scanning to quantify skeletal muscle index (sarcopenia) has become a potent prognostic predictor that may also guide the degree of nutritional intervention.

On the basis of this assessment, an individualized and dynamic treatment plan is developed. This treatment plan is on a continuum of care:

- Diet Counseling: Providing evidence-based education regarding individual needs, such as achieving protein targets, adopting a Mediterranean-style eating pattern, and managing side effects.
- Oral Nutritional Supplements (ONS): Writing high-calorie, high-protein supplements for patients who cannot meet their requirements through food.

Table 2. Practical Nutritional Management of Common Immune-Related Adverse Events (irAEs).

irAE	Nutritional Goals	Practical Dietary Strategies
Colitis/Diarrhea	Reduce bowel frequency & inflammation; maintain hydration and electrolyte balance; rehabilitate microbiome post-flare.	**Acute phase:** Implement a low-residue diet (e.g., white bread, white rice, bananas, applesauce). Consider a short-term, supervised low-FODMAP diet. Strictly avoid caffeine, alcohol, spicy foods, and high-fat foods. **Recovery phase:** Systematically reintroduce soluble fiber (e.g., oats, psyllium) to restore microbial diversity and function.
Hepatitis	Reduce metabolic stress on the liver; support hepatic regeneration.	Limit intake of saturated and trans fats. Ensure moderate, high-quality protein intake. Base meals on complex carbohydrates and non-cruciferous vegetables. Complete avoidance of alcohol is mandatory.
Fatigue/Anorexia	Maximize nutrient and calorie intake with minimal volitional effort; prevent catabolism.	Advocate for small, frequent meals and snacks (every 2-3 hours). Utilize nutrient-dense, high-protein smoothies and medical oral nutritional supplements. Keep easy-to-consume foods available. Prioritize patient food preferences to enhance palatability.
Nausea/Vomiting	Settle the stomach; prevent dehydration and nutrient deficits.	Recommend small portions of bland, dry foods (crackers, toast, pretzels). Suggest ginger tea, ginger ale, or ginger candies. Encourage cool, clear liquids consumed separately from solid meals.

- Enteral Nutrition (EN): Initiating tube feeding in patients with a functional gastrointestinal tract but who are not getting an adequate amount through the mouth, for example, those with severe dysphagia or anorexia.
- Parenteral Nutrition (PN): Turning to intravenous nutrition only if the gut is either non-functional or inaccessible, as it is riskier and more costly.

In this process, the oncology nurse is a key frontline clinician. They are often the first to detect an alteration in the nutritional status of a patient, provide initial reinforcing education, and serve as the critical link between the patient, the oncologist, and the dietitian, with a stable and integrated supportive care team (Lockwood et al., 2023). Figure 2 illustrates the integrative nutritional strategy to enhance immunotherapy outcomes.

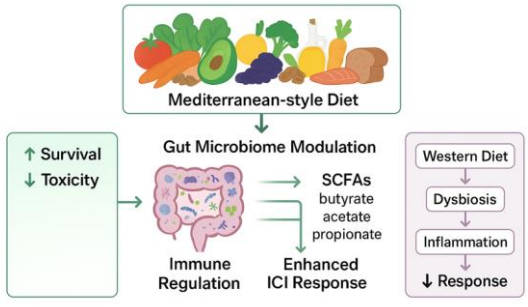

Figure 2. Integrative Nutritional Strategy to Enhance Immunotherapy Outcomes.

Conclusion and Future Research

The cumulative evidence of this review strongly establishes that host nutritional status is not a passive background variable but an active and modifiable variable that importantly interplays with cancer immunotherapy efficacy and toxicity. The clinical model is therefore shifting away from a reactive nutrition-as-palliation model to an active one in which it is being positioned as an integral component of the treatment regimen itself. A fundamental cachexia prevention and treatment strategy through adequate energy and protein intake, overlaid with a high plant food diet, fermentable fiber, healthy fats, and fermented foods, synergistically works to create a systemic metabolic and inflammatory state, and a gut microbiome, which is optimally set for an optimal anti-tumor immunologic response.

Even though these exciting correlations exist, the science of immuno-nutrition remains in the developmental stage. In order to move forward from correlation to causation and to establish solid, evidence-based nutritional prescriptions, there has to be an emerging new generation of strong research. Upcoming research needs to give high emphasis to large-scale, prospective, randomized controlled dietary intervention trials that test hypotheses explicitly, like between a Mediterranean diet intervention and standard nutritional advice, with ICI response rates, survival, and irAE rates as main outcomes. There is also an urgent necessity to more clearly define the precise molecular pathways through which particular food components, their effects on the gut microbiome and its metabolome, and consequent effects on systemic and anti-tumor immunity are interconnected. The eventual goal is to move toward individually tailored nutritional recommendations specific to one's unique gut microbiome composition, tumor immunophenotype, and genotype.

Meanwhile, current evidence is sufficient to warrant the instant use of proactive nutritional care. A

multidisciplinary team with a working partnership between the patient, oncologist, nurse, and registered dietitian is no longer an option but a necessity to unlock the full therapeutic potential of nutrition for maximizing survival and quality of life of this cancer-transformed patient.

References

1. Argilés, J. M., Busquets, S., Stemmler, B., & López-Soriano, F. J. (2014). Cancer cachexia: understanding the molecular basis. *Nature Reviews Cancer*, *14*(11), 754-762.https://doi.org/10.1038/nrc3829
2. Avery, J. C., & Hoffmann, P. R. (2018). Selenium, selenoproteins, and immunity. *Nutrients*, *10*(9), 1203. https://doi.org/10.3390/nu10091203
3. Berger, A. M., Mooney, K., Alvarez-Perez, A., Breitbart, W. S., Carpenter, K. M., Cella, D., ... & Smith, C. (2015). Cancer-related fatigue, version 2.2015. *Journal of the National Comprehensive Cancer Network*, *13*(8), 1012-1039. https://doi.org/10.6004/jnccn.2015.0122
4. Bolte, L. A., Lee, K. A., Björk, J. R., Leeming, E. R., Campmans-Kuijpers, M. J., De Haan, J. J., ... & Weersma, R. K. (2023). Association of a mediterranean diet with outcomes for patients treated with immune checkpoint blockade for advanced melanoma. *JAMA oncology*, *9*(5), 705-709. doi:10.1001/jamaoncol.2022.7753
5. Bourke, C. D., Berkley, J. A., & Prendergast, A. J. (2016). Immune dysfunction as a cause and consequence of malnutrition. *Trends in immunology*, *37*(6), 386-398. https://doi.org/10.1016/j.it.2016.04.003
6. Chandler, P. D., Chen, W. Y., Ajala, O. N., Hazra, A., Cook, N., Bubes, V., ... & VITAL Research Group. (2020). Effect of vitamin D3 supplements on development of advanced cancer: a secondary analysis of the VITAL randomized clinical trial. *JAMA network open*, *3*(11), e2025850-e2025850. doi:10.1001/jamanetworkopen.2020.25850
7. Cortellini, A., Bozzetti, F., Palumbo, P., Brocco, D., Di Marino, P., Tinari, N., ... & Porzio, G. (2020). Weighing the role of skeletal muscle mass and muscle density in cancer patients receiving PD-1/PD-L1 checkpoint inhibitors: a multicenter real-life study. *Scientific reports*, *10*(1), 1456. https://doi.org/10.1038/s41598-020-58498-2
8. Davar, D., Dzutsev, A. K., McCulloch, J. A., Rodrigues, R. R., Chauvin, J. M., Morrison, R. M., ... & Zarour, H. M. (2021). Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients. *Science*, *371*(6529), 595-602. https://doi.org/10.1126/science.abf3363
9. Deutz, N. E., Bauer, J. M., Barazzoni, R., Biolo, G., Boirie, Y., Bosy-Westphal, A., ... & Calder, P. C. (2014). Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. *Clinical nutrition*, *33*(6), 929-936. https://doi.org/10.1016/j.clnu.2014.04.007
10. Flint, T. R., Fearon, D. T., & Janowitz, T. (2017). Connecting the metabolic and immune responses to cancer. *Trends in molecular medicine*, *23*(5), 451-464. https://doi.org/10.1016/j.molmed.2017.03.001
11. Fodil, M., Blanckaert, V., Ulmann, L., Mimouni, V., & Chénais, B. (2022). Contribution of n-3 long-chain polyunsaturated fatty acids to the prevention of breast cancer risk factors. *International Journal of Environmental Research and Public Health*, *19*(13), 7936. https://doi.org/10.3390/ijerph19137936
12. Gopalakrishnan, V., Spencer, C. N., Nezi, L., Reuben, A., Andrews, M. C., Karpinets, T. V., ... & Wargo, J. (2018). Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. *Science*, *359*(6371), 97-103. https://doi.org/10.1126/science.aan4236
13. He, Y., Fu, L., Li, Y., Wang, W., Gong, M., Zhang, J., ... & Guo, X. (2021). Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic CD8+ T cell immunity. *Cell metabolism*, *33*(5), 988-1000. https://doi.org/10.1016/j.cmet.2021.03.002
14. Koh, A., De Vadder, F., Kovatcheva-Datchary, P., & Bäckhed, F. (2016). From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell*, *165*(6), 1332-1345. https://doi.org/10.1016/j.cell.2016.05.041
15. Lee, K. A., Luong, M. K., Shaw, H., Nathan, P., Bataille, V., & Spector, T. D. (2021). The gut microbiome: what the oncologist ought to know. *British journal of cancer*, *125*(9), 1197-1209. https://doi.org/10.1038/s41416-021-01467-x
16. Lockwood, A. B., Klatka, K., Parker, B., & Benson, N. (2023). Administration and Scoring Errors on the Woodcock–Johnson IV Tests of Achievement: Before and During COVID-19. *Journal of Psychoeducational Assessment*, *41*(5), 501-513. https://doi.org/10.1177/07342829231166725
17. Luu, M., Pautz, S., Kohl, V., Singh, R., Romero, R., Lucas, S., ... & Visekruna, A. (2019). The short-chain fatty acid pentanoate suppresses autoimmunity by modulating the

metabolic-epigenetic crosstalk in lymphocytes. *Nature communications*, *10*(1), 760. https://doi.org/10.1038/s41467-019-08711-2

18. Mleczko-Sanecka, K., & Silvestri, L. (2021). Cell-type-specific insights into iron regulatory processes. *American Journal of Hematology*, *96*(1), 110-127. https://doi.org/10.1002/ajh.26001
19. Mondul, A. M., Weinstein, S. J., Layne, T. M., & Albanes, D. (2017). Vitamin D and cancer risk and mortality: state of the science, gaps, and challenges. *Epidemiologic reviews*, *39*(1), 28-48. https://doi.org/10.1093/epirev/mxx005
20. Muscaritoli, M., Arends, J., Bachmann, P., Baracos, V., Barthelemy, N., Bertz, H., ... & Bischoff, S. C. (2021). ESPEN practical guideline: Clinical Nutrition in cancer. *Clinical nutrition*, *40*(5), 2898-2913. https://doi.org/10.1016/j.clnu.2021.02.005
21. Munteanu, C., & Schwartz, B. (2022). The relationship between nutrition and the immune system. *Frontiers in nutrition*, *9*, 1082500. https://doi.org/10.3389/fnut.2022.1082500
22. Penna, F., Ballarò, R., Beltrà, M., De Lucia, S., García Castillo, L., & Costelli, P. (2019). The skeletal muscle as an active player against cancer cachexia. *Frontiers in physiology*, *10*, 41. https://doi.org/10.3389/fphys.2019.00041
23. Peterson, S. J., & Mozer, M. (2017). Differentiating sarcopenia and cachexia among patients with cancer. *Nutrition in clinical practice*, *32*(1), 30-39. https://doi.org/10.1177/0884533616680354
24. Postow, M. A., Callahan, M. K., & Wolchok, J. D. (2015). Immune checkpoint blockade in cancer therapy. *Journal of clinical oncology*, *33*(17), 1974-1982. https://doi.org/10.1200/JCO.2014.59.4358
25. Radzikowska, U., Rinaldi, A. O., Çelebi Sözener, Z., Karaguzel, D., Wojcik, M., Cypryk, K., ... & Sokolowska, M. (2019). The influence of dietary fatty acids on immune responses. *Nutrients*, *11*(12), 2990. https://doi.org/10.3390/nu11122990
26. Ribas, A., & Wolchok, J. D. (2018). Cancer immunotherapy using checkpoint blockade. *Science*, *359*(6382), 1350-1355. https://doi.org/10.1126/science.aar4060
27. Routy, B., Le Chatelier, E., Derosa, L., Duong, C. P., Alou, M. T., Daillère, R., ... & Zitvogel, L. (2018). Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. *Science*, *359*(6371), 91-97. https://doi.org/10.1126/science.aan3706
28. Schwingshackl, L., & Hoffmann, G. (2014). Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies. *International journal of cancer*, *135*(8), 1884-1897. https://doi.org/10.1002/ijc.28824
29. Shiroyama, T., Nagatomo, I., Koyama, S., Hirata, H., Nishida, S., Miyake, K., ... & Kumanogoh, A. (2019). Impact of sarcopenia in patients with advanced non–small cell lung cancer treated with PD-1 inhibitors: A preliminary retrospective study. *Scientific reports*, *9*(1), 2447. https://doi.org/10.1038/s41598-019-39120-6
30. Spencer, C. N., McQuade, J. L., Gopalakrishnan, V., McCulloch, J. A., Vetizou, M., Cogdill, A. P., ... & Wargo, J. A. (2021). Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science*, *374*(6575), 1632-1640. https://doi.org/10.1126/science.aaz7015
31. Tang, L., Wang, J., Lin, N., Zhou, Y., He, W., Liu, J., & Ma, X. (2021). Immune checkpoint inhibitor-associated colitis: from mechanism to management. *Frontiers in immunology*, *12*, 800879. https://doi.org/10.3389/fimmu.2021.800879
32. Torres, W., Pérez, J. L., Diaz, M. P., D'Marco, L., Checa-Ros, A., Carrasquero, R., ... & Bermudez, V. (2023). The role of specialized pro-resolving lipid mediators in inflammation-induced carcinogenesis. *International Journal of Molecular Sciences*, *24*(16), 12623. https://doi.org/10.3390/ijms241612623
33. Weenink, B., French, P. J., Sillevis Smitt, P. A., Debets, R., & Geurts, M. (2020). Immunotherapy in glioblastoma: current shortcomings and future perspectives. *Cancers*, *12*(3), 751. https://doi.org/10.3390/cancers12030751
34. Wessels, I., Maywald, M., & Rink, L. (2017). Zinc as a gatekeeper of immune function. *Nutrients*, *9*(12), 1286. https://doi.org/10.3390/nu9121286