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Literature Review

Nutrition in Hematology Gene and Cellular Therapy: What to Do?

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Abstract

There is a lack of information about nutrition in hematology gene and cellular therapy. The role of nutrition is essential because malnutrition, obesity, and nutrient deficiency are strongly associated with damage to the immune system. A search was conducted on 10 July 2022 using PubMed, comprised of over 33 million citations for biomedical literature from MEDLINE, life science journals, and online books. Databases were screened for search terms in titles and abstracts referring to nutrition, nutrition intervention, gene therapy, Chimeric Antigen Receptor (CAR)-T cell Therapy, and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). This report summarizes interventional nutrition studies in oncology and hematology settings and describes possible nutritional interventions to improve gene and cellular therapy outcomes. The impact of nutrition evaluation and intervention needs to be studied prospectively**.**

Keywords: *Nutrition; Genic Therapy; Car-T Cell; Zinc; Vitamin D; Microbiota; Omega 3*

Introduction

Nutritional balance is essential for achieving systemic homeostasis and maintaining normal physiology, a significant challenge for living organisms. Therefore, processes are developed to control systemic nutrient utilization and storage in adipose tissue, liver, and muscle. Anabolic and catabolic processes are essential for an organism to live [1,2].

The nutrition imbalance that damages the immune system is one of the most energy-consuming in the body [2]. The secretion of hormones and cytokines from adipose tissue (adipocytokines) has crucial immune signaling functions and responses. Accordingly, obesity and malnutrition have negatively affected the immune system, increasing infection risk due to having more or less fatty tissue [2].

Obesity has been associated with greater susceptibility to infections (H1N1, influenza, pneumonia, sepsis, etc.); more days in the Intensive Care Unit; more complications in SARSCOV-19; lower antibody formation in flu, hepatitis B, and tetanus vaccines [1-3]. In addition, malnutrition has increased the risk of infections and complications, reduced glucose metabolism, and GLUT1 expression in the T cell [1,2].

Although nutrition has been strongly associated with immune response, there is a lack of studies and guidelines about nutritional intervention in hematology gene and cellular therapy. We believe that is a fundamental issue. Our objective was to discuss possibilities in nutrition therapy for these patients.

Methods

Literature search and study selection

On 08 March 2023, a search was conducted using PubMed, comprised of over 33 million citations for biomedical literature from MEDLINE, life science journals, and online books. Databases screened for search terms in titles and abstracts referring to "nutrition", "nutrition intervention", "gene therapy", "Chimeric Antigen Receptor (CAR) -T cell Therapy", and "Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)".

We used the pre-specified inclusion criteria were adult patients, studies about nutrition, nutrition intervention, gene therapy, CRISPR, Cart-T cell, zinc, vitamin D, microbiota, immune nutrients, and calcium, and full-text articles in English. And the exclusion criteria were patients ≤18 years old and non-full-text articles in a language other than English.

Of the 2198 nutrition studies identified in the literature search, we excluded 2175 because they did not relate to the immune system and gene and cellular therapy. Therefore, we used only 23 studies about nutrition, and immune system, and hematology and only 1 study about nutrition and Car T-cell for this review.

Data extraction for review

Data were extracted for the following outcomes: "gene therapy and nutrition and hematology," "Car-T cell and nutrition," "CRISPR and nutrition and hematology," "gene therapy and immune nutrient and hematology," and "cellular therapy and nutrition".

We found no reports regarding "nutrition intervention protocols", "gene" and "cellular therapy guidelines". This report discusses possible interventional nutrition studies for these brand-new hematology treatments.

Discussion

Gene and cellular therapy

Obesity

Adipose tissue has secreted cytokines and hormones, such as tumor necrosis factor-alpha (TNF-α), which is a well-known pro-inflammatory cytokine essential for the acute phase reaction [1]. Your expression has increased during obesity and decreased following weight loss. Besides, it has been associated with insulin resistance in high-fat diet-induced obesity [1]. In addition to interleukin-6 (IL-6), adipocytes, macrophages, pre-adipocytes, and T cells have been secreted by adipose tissue [1].

In obesity, adipokines such as leptin, resistin, and visfatin, and pro-inflammatory cells, such as macrophages, pro-inflammatory neutrophils, and mast cells, have increased and promoted inflammation. In contrast, the adipokine adiponectin has been decreased and suppressed inflammatory response. The resistin has stimulated the production of TNF-α and IL-12 in macrophages, and visfatin has enabled the production of TNF-α, IL-1β, and IL-6 [1,2].

In the elderly, a high-fat and caloric diet associated with obesity cause a decline in thymic function, reducing the output of TCR diversity and naive T cells [4].

However, eosinophils, natural killer T cells (NKT cells), and ILC2 cells have been essential in the modulation of immune responses that have been reduced in obese patients. On the other hand, malnutrition has modified adipokines' secretion, decreasing immune cell activation [1].

Although more studies are necessaries, probably, patients with obesity have chemotherapy-resistant or refractory diseases, and CAR T-cell therapy may provide substantial benefits for obesity [5].

Malnutrition

A lack of intake or uptake of nutrition, leading to decreased fat-free mass and body cell mass impairs the disease's clinical outcomes and has been known as malnutrition [4]. This state requires attention once it increases the mortality risk [6,7].

Immune cells, sensitive to nutrient deprivation, have insignificant energy stores, such as glycogen. Primarily, they depend on the uptake of nutrients from their environment to fulfill their energetic necessities. Malnutrition patients have a substantial and fast decrease in splenocytes, thymocytes, and lymphocytes, mainly T cells. Besides, the reduction of immune cell function and increased risk of infectious disease have been reducing fat stores [2].

In malnutrition, leptin is a critical link between nutrition and immune cell biology. Expression of the leptin receptor has been upregulated following T-cell activation. Here we will review findings that demonstrate leptin signaling is required to license pro-inflammatory/effector T cells for activation metabolically. Changes in adipokine levels mediate communication between nutritional status and T-cell immunity. In addition, low levels of leptin have been associated with elevated death rates from infectious diseases [2].

We observed in CART cell therapy, that there is a tendency to lose 11 - 20% of weight and patients ≥ 50 years with malnutrition to increase the length of stay, there are few conclusive studies about this issue [6]. This therapy has intense inflammation [6]. However, we did not find any study about obesity.

Table 1 summarizes the immune system alteration in patients with obesity and malnutrition.

Table 1: System immune in patients with obesity and malnutrition(1,2)

	OBESITY	MALNUTRITION	IMMUNE FUNCTION
LEPTIN	HIGH	LOW	Pleiotropic hormone with many targets and many functions in immune cells Induces Th1 and Th17 polarization Polarization
Adiponectin	LOW	UNKNOWN	Polarization of monocytes and macrophages toward M2 phenotype Suppresses NK cell, eosinophil, neutrophil, γδ T cell, and dendritic cell activation and inflammatory cytokine production
T cell Glut1 expression	LOW		Modulating and improving insulin resistance
The proportion of Treg cell	HIGH	LOW	Altering macrophage polarization
Number and function of Teff cell	LOW	HIGH	Producing IL-6 and IFN-g, which leads to functional plasticity of Treg cells
B cells TNFα M1 macrophages CRP IL-1RA IL-1β MIP-1α,MIP-1β	HIGH	UNKNOWN	Neutrophil chemotaxis Inhibits IL-1α and IL-1β activity Stimulates macrophage activity Enhances macrophage migration Stimulates the production of TNF-α, IL-1β, and IL-6
IL 6	HIGH	LOW	Recruitment of macrophages; polarization toward pro-inflammatory classically activated macrophages Induces
MCP1	HIGH	HIGH	Macrophage recruitment Inhibits
MIF	HIGH	LOW	Inhibits macrophage migration
IL33	LOW	HIGH	Maintains adipose tissue-resident Treg cell function, promotes Th2 response, promotes alternatively activated macrophage polarization
IL8	HIGH	LOW	Induces neutrophil chemotaxis
IL-interleukin; TNFα -tumor necrosis factor-alpha; MIP-macrophage inflammatory protein. CRP-C reactive protein; MIF-macrophage migration inhibitory factor			
HIGH: High-quality prospective cohort study with adequate power or systematic review of these studies; **LOW:** Lesser quality prospective cohort, retrospective cohort study, untreated controls from an RCT, or systematic review of these studies; **UNKNOWN:** Not know evidence and studies results			

Nutrients of immunity

Healthy food has been associated with better system immune cells, mainly glutamine, glucose, amino acids, principally leucine, tryptophan, arginine and serine, and fatty acids [7].

Arginine is essential to decrease T cell dysfunction and injury; increase lymphocytic IL-2; increase tumor lysis by macrophages; increase nitric oxide formation; increase lymphocyte mitotic response; stimulate the production of G.H.; T-helper cell increase [8,9].

Fatty acids omega 3 is related to reduced cytokine response to inflammation; the decreased ability of leukocytes to produce inflammatory cytokines; the action of prostaglandins and leukotrienes; natural killer, and T cell mediation. Besides, nucleotides improve T-cell function [8,9].

Metabolically T cells have been affected by [10]:

1. **Substrate transport:** Reduction of amino acid transport has limited effector T cell expansion and blocking glucose uptake or inhibiting lactate export has inhibited effector T cell development. T reg could be blocked by inhibiting fatty acid uptake glycolysis.
2. **Glycolysis:** Lactate production and Inhibiting glycolysis have inhibited effector T cells, and restricting glycolysis can promote cell longevity, limit terminal differentiation, and have a memory phenotype.
3. **Fatty acid synthesis:** Reduction of fatty acid synthesis could promote T reg development and impair Th17 differentiation.
4. **Fatty acid oxidation:** Enhancing fatty acid oxidation has promoted memory cell development or Treg.
5. **Glutaminolysis:** Glutaminolysis and reductive carboxylation inhibiting glutamine metabolism have inhibited effector T cell development and T cell proliferation.
6. **Fatty:** Mitochondrial function and enhancing mitochondrial function through increasing mass, altering mitochondrial dynamics may support T cell longevity or mitochondrial oxidative phosphorylation system (OXPHOS).

In addition, some studies showed, in animal models, dietary restriction of caloric intakes, such as starvation or a fasting-mimicking diet or intermittent fasting, has been associated with enhancing anti-tumor immune function, acting mainly in $CD8^+$ T-cell and macrophages [4]. More studies in human models will be necessary to certify these findings and to define how much caloric reduction.

Microbiome

It has been responsible for producing essential vitamins and trace elements, resistance to enteropathogens, inhibiting pathogenic growth, immune response, and production of short-chain fatty acids. Besides, the microbiome has been changed by drug use (antibiotics and anti-inflammatory drugs), diet, and aging [11].

The microbiome has been classified as positive - high diversity and abundance of *Ruminococcaceae* and *Faecalibacterium* - or negative - reduced diversity and increased relative abundance of *Bacteroidales*. In oncology, a positive microbiome stimulates a systemic and anti-tumor immune response. It has therapeutic potential in immunotherapy and CART cells [12,13].

According to Spencer., *et al*. [14], a balanced diet rich in fibers had better immunotherapy results than probiotic use because a healthy diet promotes a favorable microbiome with high diversity.

Vitamin D

Vitamin D has been associated with antimicrobial, anti-inflammatory, and antioxidant effects; maintenance of functional and structural integrity of mucosal cells in innate barriers; normal functioning of T cells; antibody production and antigen responses; reduction of the respiratory tract and lung infection risk; alleviation of the inflammatory response is an adequate immunoregulatory function [15,16].

The serum levels of vitamin D and BMI ≥ 30 kg/m^2 have been inversely proportional, explained by the body fat kidnap the fat-soluble vitamin [15]. Moreover, vitamin D deficiency is common among the elderly. We found low levels of vitamin D in 5% to 25% of the independent elderly and 60 to 80% of institutionalized patients [14]. This is important because low levels of vitamin D have contributed to the reduction of immune tolerance and organ-specific or systemic autoimmune diseases associated with mechanisms that finally progress to T cells or reactive B [16].

Low vitamin D levels were associated with lower cell viability of the infused CAR-T product, the worst 100-day complete response, and low overall survival [17]. Besides, gut microbial metabolites and ligands have modified CAR-T cells and T cells. T cell differentiation and change effector functions depend on bile acid metabolites acting on vitamin D receptors in the intestinal mucosa [15]. Important emphasis on supplement nutrients for treating deficiencies is essential; however, in patients with normal levels could cause side effects, such as fractures in unnecessary vitamin D supplementation [18].

Calcium

The symptoms of cytokine release syndrome (CRS), which is one important complication of CAR-T cell therapy, are very similar to calcium deficiency [19,20]. CRS has neurological symptoms: headaches, confusion, hallucinations, delirium, aphasia, paresis, and seizures [19]. Similarly, hypocalcemia has seizures, confusion, disorientation, and paresthesia [21]. For this reason, in clinical practice, there is a suggestion for evaluating hypocalcemia in these patients as a differential diagnosis of CRS.

Zinc

Zinc, indispensable for diverse cell functions, is an important trace element and a cofactor of an estimated 3000 human proteins. Zinc deficiency acts on the immune system, such as T-cell development and activation. Therefore, zinc level restoration improves immune function and decreases the incidence of infections in patients with zinc deficiency [22,23]. This nutrient might be evaluated in gene and cellular treatment patients.

Nutrition approach in hematology gene and cellular therapy

Gene and cellular therapy are brand-new; therefore, there are few studies about the nutrition approach. Based on our discussion, we believe that obesity and malnutrition could be prognostic factors in these therapies. Immunonutrition, vitamin D, zinc, and calcium are essential for the immune system and should be evaluated before and during these treatments.

A positive microbiome is associated with a healthy and balanced diet; therefore, our patients should have this nutrition recommendation. Use or not-use probiotics must be more studied as an attractive strategy in this group.

Conclusion

In conclusion, editing and cellular therapy are costly, so every strategy is important. Nutrition is considered a non-expensive and practical intervention, hence must be more studied to improve prognosis and reduce complications.

Conflicts of Interest

None.

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