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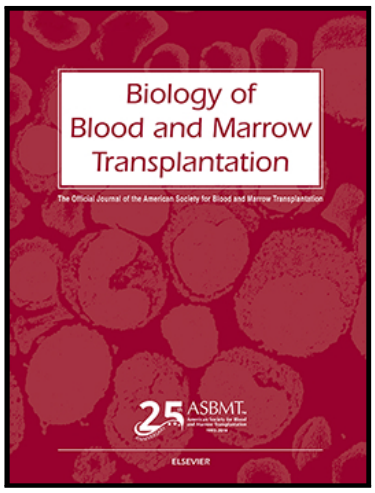

Challenging and Practical Aspects of Nutrition in Chronic Graft-versus-host Disease

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Highlights

- There are few studies on nutrition and chronic GVHD.
- Many drugs used to treat chronic GVHD lead to nutritional problems and metabolic syndrome.
- Monitoring and early nutritional measures of metabolic syndrome, osteoporosis and loss of muscle mass could improve the outcome and response to treatment in these patients.
- Zinc, vitamin A, vitamin D, omega 3 and probiotics could contribute to symptom reduction and nutritional improvement.

Challenging and Practical Aspects of Nutrition in Chronic Graft-versus-host Disease

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Abstract:

There is a lack of information about nutrition in chronic graft-versus-host disease (GVHD). The role of nutrition is important because malnutrition is strongly associated with severe chronic GVHD manifestations. There is a high prevalence of metabolic syndrome and osteoporosis in this setting. This study reviews the literature, describes main aspects of nutrition and discusses about macronutrients (i.e. vitamins), micronutrients (i.e. Mg, Zn, Ca and K) and supplements (probiotics and omega 3 fatty acids). A search was carried out in March 2020 using PubMed. Databases were screened for searching terms in titles and abstracts, referring to chronic GVHD, nutrition intervention, protein, and body composition. Data were extracted for the following outcomes: nutrition, nutrition intervention, chronic GVHD, nutrition deficiencies, diet, vitamin, dry eye, probiotic, protein and body composition. In this report, we summarize interventional nutrition studies reported in oncology and metabolic syndrome settings and describe our nutritional clinical practice in hematopoietic cell transplant and chronic GVHD. The impact of nutrition evaluation and intervention on muscle mass loss, dry eye, dysgeusia, metabolic syndrome, osteoporosis and comorbidities associated with chronic GVHD need to be studied prospectively.

Key words:

Nutrition; GVHD; protein; vitamins; ω3 fatty acids; probiotics

Introduction:

Chronic graft-versus-host disease (GVHD) occurs in 30% to 70% of allogeneic stem cell transplant recipients and represents a major cause of morbidity and late mortality. (1,2) Chronic GVHD is a syndrome that can affect the skin, mouth, eye, muscle, fascia, joints, gastrointestinal tract (GIT), liver and lungs resembling autoimmune and other immunologic disorders such as scleroderma, Sjogren's syndrome, primary biliary cirrhosis, bronchiolitis obliterans or immune cytopenia.(1,2)

Anorexia, dysgeusia, xerostomia, early satiety, pancreatic insufficiency and weight loss are complications of chronic GVHD that can lead to malnutrition and cachexia and impact functional and overall health status. (2–4) Weight reduction severity of chronic GVHD, elevated resting energy expenditure and serum tumor necrosis factor-α are risk factors associated with increased mortality among chronic GVHD patients.(5,6)

The nutrition evaluation in chronic GVHD is important because malnutrition is strongly associated with severe chronic GVHD manifestations and quality-of-life impairment.(2,6)

The role of nutritional evaluation and interventions has been well established in the early posttransplant phase and in patients with acute GVHD (7), however there are few small studies in chronic GVHD. (2,4,5) Thus, we reviewed and discussed nutrition intervention strategies reported in oncology and metabolic syndrome studies. (7,8)

This study reviews the literature and describes clinical practice aspects of nutrition in chronic GVHD.

Methods:

Literature search and study selection

A search was carried out on 18 March 2020 using PubMed, which is comprised of over 28 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 chronic GVHD, nutrition intervention, protein, and body composition.

The pre-specified inclusion criteria were patients with chronic GVHD, nutrition intervention (vitamins, micronutrients, prebiotics, probiotics, omega 3 and omega 6 fatty acids) and full text article in the English language. The exclusion criteria were patients with acute GVHD or non-chronic GVHD, without nutrition interventions and with full text articles in languages other than English.

Of the 321 nutrition studies identified in the literatures search, we excluded 243 either because they related to acute GVHD only or because the reports did not specifically indicate chronic GVHD as part of the study. Therefore, 78 studies in patients with chronic GVHD were identified and used for this review.

Data extraction for review

Data were extracted for the following outcomes: nutrition, nutrition intervention, chronic GVHD, nutrition deficiencies, diet, vitamin, dry eye, probiotic, protein, and body composition.

We found no reports regarding nutrition intervention and guidelines in chronic GVHD. In this report we discuss interventional nutrition studies reported in oncology(8), in metabolic syndrome(7), and describe our clinical nutritional practice in hematopoietic cell transplant(HCT) and in patients with chronic GVHD.

Discussion:

A- Nutrition and chronic GVHD

Nutrition intervention in chronic GVHD patients is a challenge because of the number of organ systems involved and side effects of the treatment leading to metabolic syndrome. (**Table1)** (9)

Weight loss is a significant problem in chronic GVHD, but there are few studies about its prevalence. In this review, we found wasting and cachexia in severe stages have been associated with increased numbers of infections, decubitus ulcers, and death. (5,10) The diagnosis of malnutrition is complex, including low muscle mass, phenotypic and etiologic criteria.(11)

Muscle loss and weight gain can be exacerbated by high-dose or prolonged treatment with corticosteroids for managing chronic GVHD and the use of antiviral drugs to prevent infectious complications.(12) As indicated above, treatment with the use of calcineurin inhibitors and sirolimus can result in increased serum cholesterol and triglyceride concentrations (12) and glucocorticoid therapy is associated with hyperglycemia. (6)

Many chronic GVHD manifestations are associated with malnutrition and weight loss. Oral GVHD, mainly dysphagia, oral sensitivity, heat/cold intolerance and oral swelling, causes difficulty in eating and drinking, resulting in decreased calorie and protein intake. Gastrointestinal GVHD manifestations include dysphagia, nausea, vomiting, malabsorption (diarrhea), anorexia as well as early satiety. Lung GVHD results in wasting syndrome and increased energy expenditure. Along with gastrointestinal complications, these symptoms may result in weight loss and malnutrition. (5,6)

The primary therapeutic of patients with chronic GVHD is the use of corticosteroids with a median duration between 2 to 3 years. (13) It results in a reduction in muscle mass, which is known to be associated with decreased performance status and fatigue.(14)

Fatigue is a common symptom in chronic GVHD and negatively affects quality of life. There is no targeted nutrition intervention shown to improve fatigue associated with imbalanced energy intake, metabolism and expenditure, malnutrition, sarcopenia and cachexia. (15)

B- Body composition evaluation

Loss of muscle mass and sarcopenia is strongly associated with mortality in cancer patients, as well as complications of cancer surgery and dose-limiting toxicity during systemic anti-cancer therapy. (8)

Sarcopenia is a progressive and general loss of muscle mass, function and strength. (16) Because of the already mentioned prolonged treatment with corticosteroids in chronic GVHD, evaluation of sarcopenia and muscle loss is important. (13) Therefore, an appropriately increased

physical activity aimed to maintain or gain muscle mass is imperative in this population.(8)

In the last years many studies have shown the importance of body composition parameters evaluated by Bioelectrical impedance analysis, Dual energy x-ray absorptiometry and Computerized Tomography in HCT outcomes, such as mortality and GVHD. (17–21). Regardless of the method chosen, the diagnosis of sarcopenia and low muscle mass can be made through the analysis of hand-grip strength, appendicular skeletal muscle mass and mid upper-arm muscle area. (**Table 2**) (8,11,16,22)

C- Nutrition intervention

1. Oral supplements and nutritional intake

There are very few studies concerning specific recommendations regarding general nutritional intake and oral supplements during chronic GVHD.

In oncology and HCT, patients frequently have elevated nutrient requirements and altered carbohydrate, fat, and protein metabolism. (23) They require modified diets, oral supplements, or nutrition support therapy to prevent malnutrition. (23) In general, we use the same calorie and protein intake recommended during HCT, respectively 25-30 kcal/kg of body weight and 1.5-2.0 g protein/ kg of body weight. (8,9)

There are few studies about nutrition recommendations for obese cancer patients. In our clinical practice, for patients with chronic GVHD who are obese (Body mass index(BMI)≥30 kg/m^2), the calorie intake suggested is <14 kcal/kg of actual weight or 22-25 kcal/kg of ideal weight and protein

intake is 1.5-2.0 g/kg of actual weight or 2.0-2.5 g/kg of ideal weight. (**Table 3**) (24–26)

Nutrition evaluation and support must be provided to malnourished patients and those at nutritional risk, especially when oral energy intake has already been insufficient or expected to be inadequate (<50% of estimated caloric requirements) ≥ 7 days. (11,27) Oral supplements may be recommended at this time due to their proven efficacy in increasing protein-calorie intake. (27)

Homemade or industrial oral nutritional supplements are homogeneous, and usually nutritionally complete nutrient mixtures for oral consumption and are most often recommended to supplement volitional food intake.(8)

2. Vitamins and nutrients

2.1 Vitamin A

Vitamin A (VA) is an important factor for maintaining immune homeostasis and is obtained from a diet containing carotenoids (plants) or retinyl esters (animal products). Retinyl esters are the primary storage form of VA in the body while carotenoids are absorbed in the intestines and can be converted to retinol. Retinol is necessary for the synthesis of epithelial cell RNA and glycoprotein synthesis on the ocular surface. (28,29)

VA deficiency has a wide range of ocular manifestations, including conjunctival and corneal xerosis, keratomalacia, retinopathy, visual loss, and nyctalopia. (28) In addition VA deficiency impairs anti-pathogen

immunity and is associated with increased susceptibility to infections.(29) **Table 4** presents the daily recommendation, diagnosis and treatment.

A recent study demonstrated a positive association between low VA levels with the severity of ocular manifestations in patients with chronic GVHD. (28) These results suggested that VA may be implicated in the pathogenesis of ocular manifestations associated with chronic GVHD. (28)

Other studies have demonstrated VA may also play a role in non-ocular manifestations, such as development and severity of chronic GVHD. (29) In liver related chronic GVHD manifestations, serum levels of VA may be significantly reduced because of abnormal metabolism. (28)

2.2 Vitamin D

Vitamin D (VD) is a nutrient whose sources can be UVB-dependent endogenous production, supplementation and dietary intake. There are two major forms of VD, cholecalciferol(synthesized in the human skin) or ergocalciferol. (30,31)

VD through 1.25 (OH) secretion acts locally on T and B lymphocytes. In addition, the stimulation of its receptor leads to the modification of cytokine secretion by direct interaction with promoter elements responsive to VD and, perhaps, indirectly, through interaction with other transcription factors.(32)

Studies have shown a positive correlation between VD deficiency and risk of chronic GVHD, more commonly in obese and malnourished patients.(33,34) In addition to the decreased severity and occurrence of relapse, reduced progression and death were associated with high serum levels of VD in chronic GVHD.(35,36) However, some studies did not find

any correlation between low levels of VD and symptoms of chronic GVHD and/or prognosis.(31,34) **Table 4** shows the daily recommendation, diagnosis and treatment.

2.3 Zinc

Zinc is a trace element and a cofactor of an estimated 3000 human proteins, which is indispensable for diverse cell functions, including growth and differentiation. Therefore, zinc deficiency affects highly proliferating systems such as the immune system, especially zinc-dependent processes such as T-cell development and T-cell activation. For this reason, zinc level restoration improves immune function in patients with zinc deficiency and decreases the incidence of infections.(37)

Zinc is also responsible for taste perception, healing and the integrity of gastrointestinal mucosa, which is important in the defense against intestinal infections. Its deficiency can be caused by chronic diarrhea and malabsorption, a consequence of GVHD. (38–40)

Several studies recommended zinc supplementation in patients with GVHD because it is relevant for the treatment of recurrent lesions. (4,39) It has been suggested that zinc supplementation (up to 3 doses of 45mg ZnSO4 per day) is safe and effective for treating taste perception. (39,41) **Table 4** presents the daily recommendation, diagnosis and treatment.

2.4 Magnesium

Magnesium is the second most abundant intracellular and fourth extracellular cation in the body. (42) It is required for all enzymatic reactions involving adenosine triphosphate and kinases, neuromuscular excitability, cell permeability, regulation of ion channels, mitochondrial function, cellular proliferation and apoptosis and immunity.(42,43)

The treatment of hypomagnesemia is based on its severity, in general symptoms occur when magnesium level < 1mEq/l. (44) **Table 4** shows the daily recommendation, diagnosis and treatment.

2.5 Potassium

Cyclosporine, tacrolimus and anti-thymocyte globulin(ATG) used in the treatment of chronic GVHD may result in hypokalemia.(9,43)

The immediate goal of treatment is the prevention of potentially life-threatening cardiac conduction disturbances and neuromuscular dysfunction by raising serum potassium to a safe level. (45,46) It is appropriate to increase dietary potassium in patients with low-normal and mild hypokalemia, particularly in those with a history of hypertension or heart disease.(45) Unfortunately, the effectiveness of increased dietary potassium is limited–because most of the potassium contained in foods is coupled with phosphate, whereas most cases of hypokalemia involve chloride depletion and respond best to supplemental potassium chloride. (45) **Table 4** presents the daily recommendation, diagnosis and treatment.

3. Omega 3 fatty acids

Polyunsaturated fatty acids (PUFAs) include a group of compounds called essential fatty acids (EFAs). These compounds are termed “essential” because the human body needs them but lacks the appropriate enzymes for their synthesis. There are two families of EFAs: the omega-6 (n-6) family and the omega-3 (n-3) family. (47,48)

In chronic GVHD, omega 3 fatty acids are often prescribed to treat dry eye. Dry eye disease (DED) is a common and multifactorial disorder of the ocular surface, that symptoms include ocular discomfort, fatigue and visual disturbance. Unfortunately, the quality of life of patients is often extremely poor because symptoms of DED interfere with daily activities. DED patients also report having limitations, such as more pedain, and less vitality than healthy subjects. (47,49–53)

Studies describe the role of the endogenous molecules derived from the metabolism of EFAs on the ocular surface. These molecules act locally mediating inflammation. Lipoxin A4 and NPD1 are lipid autacoids formed by 12/15-LOX pathways that exhibit anti-inflammatory and neuroprotective properties, which cause an improvement of the corneal wound healing process. (47,54)

In addition, resolvins derived from n-3 EFAs are critical for their anti-inflammatory properties in ocular surface diseases, which improve tear secretion with a significant decrease of inflammation. Besides n-3 EFAs promote regulation of the immune activity to provide the optimal environment for corneal nerve regeneration. (47)

N-3 EFAs may be used alone (more usual) or in combination with n-6, however studies show different doses for combined or alone use(0.6-3.0g/day).(47,55) The most recent study, DREAM Study, used only n-3 (3.0g/day). (49)

The studies found that n-3 supplement, alone or in combination with n-6, may prevent of DED, decrease the rate of tear evaporation, osmolarity and stability and improve DED symptoms.(50,52,56–60) However, some studies showed no improvement of symptoms. (61)

4. Probiotics

Recent studies have suggested that chronic GVHD may be associated with changes in the intestinal microbiota.(62,63) Lower intestinal diversity may be associated with decreased overall survival (36% in three-year), whereas intermediate and high intestinal diversity of microbiota may show 60% and 67% overall survivals in three-year. (62)

In GVHD the microbiota has decreased health promoting species such as *faecalis bacterium*, which promote short chain fatty acid production and mark microbiota-host mutualistic configuration, as well as increase in enterococci or streptococci.(62) Also, a decrease in anaerobic bacteria and, mainly, the genus *Blautia* through antibiosis has been associated with a greater incidence of GVHD in those undergoing allogeneic HCT.(64)

Probiotics could be a treatment or a prevention for chronic GVHD in the future. However, more studies are necessary to show a clinical impact in these patients.

D- Nutrition intervention in Metabolic Syndrome and Osteoporosis

1. Metabolic Syndrome

Metabolic syndrome, prevalent in patients with chronic GVHD, is a clustering of cardiovascular risk factors, defined by the National Cholesterol Education Program Adult Treatment Panel III, this includes simultaneous occurrence of at least three of the following conditions: abdominal obesity, arterial hypertension, hyperglycemia, hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C). (65–67) It can be associated with localized lipodystrophies, high doses of steroids and high C-reactive protein, all of them present in chronic GVHD patients. (65,67,68) The main consequence of metabolic syndrome is cardiovascular risk, that increases mortality.(65)

2. Hyperglycemia and Type 2 Diabetes(T2D)

HCT has been associated with an increased risk of developing abnormalities in glycemic regulation and ultimately overt diabetes. The causes are multifactorial; nevertheless, induction of tissue insulin resistance and radiation-induced pancreatic injury have been proposed as well as total body irradiation. (66,69)

In chronic GVHD the administration of high doses and/or prolonged use of glucocorticoids is associated with development of T2D and insulin resistance. (13,65,66,68,70)

Nutrition therapy must be prescribed for all T2D patients as an effective component of the overall treatment plan. (71,72)

3. Hypertriglyceridemia (HTG) and low high-density lipoprotein cholesterol

As addressed earlier, hypertriglyceridemia can be associated with localized lipodystrophies, high doses of steroids, high C-reactive protein, all of which present in chronic GVHD patients. Nutrition is an important strategy to treat HTG. (65,67,68)

4. Osteoporosis

The prevalence of osteoporosis in chronic GVHD has been reported as high as 77%.(73–75) Risk factors for osteoporosis include calcium and VD deficiency, lower body weight, malnutrition, physical inactivity, higher glucocorticoid dose, menopause, malabsorption syndromes and chronic GVHD. (73,74)

When patients have deficiency or inadequate intake of calcium and VD in the oral diet, it is important to adjust the consumption of these nutrients according to the recommended daily doses.(76)

The goal of treatment of osteoporosis is defined as stable or increasing bone mineral density with no evidence of new fractures or fracture progression. (74) We limited our review on the nutrition interventions for the management of osteoporosis. (**Table 5**)

E- Nutritional assessment and follow-up

Based on our review, we believed that assessment should be repeated at adequate intervals to judge the requirement for nutritional intervention and to monitor its effects and outcomes. It is essential to treat, diagnose and evaluate: dietary intake, body composition, physical activity, macro and micronutrients deficiencies (vitamin A and D; zinc; magnesium;

potassium; calcium; protein) and metabolic and bone patterns. (8,28,29,31,37,42,45,46,65,67,68,70–72,74)

Institutions that care for patients with chronic GVHD patients should define nutritional standard operating, responsibilities and a quality control process. Responsibilities may be divided by specifying level 1 (performed by hematologists, nurses, and other experts with non-nutrition centered training) and level 2 (professional) nutrition-related activities. It should be an interdisciplinary mission. (8)

Many nutritional recommendations that were described in this study are used for patients without chronic GVHD. Therefore, it is unknown whether recommendations would be different for these patients. This emphasizes the need for more prospective nutritionally specific studies for this group of patients.

Conclusion

While the importance of nutrition is well known in the early posttransplant phase, there is a lack of information about the role of nutrition in chronic GVHD. The impact of nutrition evaluation and intervention on muscle mass loss, metabolic syndrome, dry eye, dysgeusia and other morbidities associated with chronic GVHD need to be studied prospectively.

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Table 1: List of side effects associated with selected drugs used in chronic GVHD (10)

Drugs	Side effects
Corticosteroids and calcineurin inhibitors	Diabetes and hyperglycemia
Calcineurin inhibitors and sirolimus	Renal dysfunction
Steroids induced (fat liver), calcineurin inhibitor, methotrexate, ibrutinib and ruxolitinib	Liver dysfunction
Mycophenolate mofetil, calcineurin inhibitor and ibrutinib	Gastrointestinal effect
Sirolimus, ruxolitinib, corticosteroids and calcineurin inhibitors	Hyperkalemia, hypomagnesemia and hyperlipidemia
Corticosteroids, calcineurin in inhibitors	Osteopenia/osteoporosis
Calcineurin inhibitor	Magnesium deficiency

Table 2: Sarcopenia cut-off points in male and female (8,13,17,18)

Method	Male	Female
Hand-Grip Strength(kgf)	<27	<18
ASM(kg)*	<20	<15
ASM/height^2(kg/m^2)*	<7.0	<5.5
MUAMA Anthropometry(cm^2)*	<32	<18

Abbreviations: ASM:appendicular skeletal muscle mass;
MUAMA: mid upper-arm muscle area
ASM(kg)= lean body mass of extremity – bone mass of extremity
ASM/height^2=ASM(kg)/ (height(m)^2
*** Bioelectrical impedance analysis and/or Dual energy x-ray absorptiometry and/or Computerized Tomography**

Table 3: Calorie and protein intake(25-27)

BMI(kg/m^2)	**Calorie Intake (kcal/kg of weight)**	**Protein intake (kcal/kg of weight)**
≤18,5	30-45	1.5-2.0
18,5<x≥29,9	25-30	1.5-2.0
≥30	<14 kcal/kg actual weight or 22-25 kcal/kg ideal weight	1.2-1.5 g/kg actual weight or 2-2.5 g/kg ideal weight
BMI: body mass index		

Table 4: Daily recommendation, Diagnosis and Treatment of nutritional deficiency (29,30,35,38-41,44,45)

Nutrient	Daily Recommendation			Deficiency diagnosis	Treatment
	Age	Male	Female		
Vitamin A	14-≥51years	900mcg RAE		<0.70 µmoles/L	vitamin A palmitate in oil 60,000 UI orally 1x/day for 2 days, followed by 4500 UI orally 1x/day
Vitamin D	14-≥ 71 years	600UI 800 UI		<20 ng/ml	50000UI D2 or D3 1x/week or 5000UI daily for 2-3 months
Zinc	14-70 years	12 mg/dia	15 mg/dia	<70 ug/dL (female) and <74 ug/dL (male)	≥3 doses of 45mg ZnSO4/day
Magnesium	14-18 years 19–30 years ≥31years	410 mg 400 mg 420 mg	360 mg 310 mg 320 mg	<1,4 mEq/L	1st day: Mg sulfate 1.0-2.0g/h iv for 3-6h 2nd day: Mg sulfate 0.5-1.0 g/h iv for 3-4 days >5th day:Magnesium oxide 2 tablest/dia
Potassium	14-≥ 51years	4,7 mg		Mild(3,0-3,4 mEq/l) Moderate(2,5-2,9mEq/l) Severe(<2,5 mEq/l)	tablets(72 mmon/day) or i.v infusion 25 ml(75 mmol/day) tablets(96 mmon/day) or i.v infusion 25 ml(100mmol/day) i.v replacement 40 mmol KCL in 1l 0.9%(glucose 5% may be used)

RAE: (1 mcg RAE = 1 mcg retinol, 2 mcg beta-carotene from supplements, 12 mcg beta-carotene from foods, 24 mcg alpha-carotene, or 24 mcg beta-cryptoxanthin)

Abbreviations: i.v: intravenous

Table 5: Nutritional intervention in Osteoporosis and Osteopenia(73)

Nutrient	Treatment
Vitamin D	* 50000UI D_2 or D_3 1x/week or 5000UI daily for 2-3 months ** Maintenance (after 2-3 months of treatment above) 1000-2000 D_2 or D_3 daily
Calcium	Male (supplements + diet) 19-50 years – 1000 mg/day 51-70 years - 1000 mg/day >70 years – 1200mg/day
Calcium	Female (supplements + diet) 19-50 years – 1000 mg/day 51-70 years - 1200 mg/day >70 years – 1200mg/day
Caffeine	To limit intake < 1 to 2 servings (8-12 ounces/serving) of caffeinated drinks per day
Alcohol	Associated with increased fracture risk Reduction of daily dose
Protein	0.8 g/kg of weight Protein supplements after hip fractures
* doses for Vitamin D deficiency (<20 ng/ml) or insufficiency (20-29 ng/ml) ** prevention dose (>30 ng/ml)	