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Anti-Inflammatory Effects of β-Glucan in Cancer Related Fatigue

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Abstract

Immune-mediated inflammatory diseases are among the exhausting diseases which are often difficult to diagnose. Fatigue is the most common syndrome accompanying cancer diseases and treatment. In cancer patients, fatigue is not only a manifestation of treatment, but also reflects biological effects of the tumor. The combination of several factors, particularly endocrinic, hematological, metabolical and detoxification strain, is connected with the acute inflammatory response. In our study, we evaluated the possible effects of supplementation with β-glucan on serum levels of CRP, SAA, orosomucoid and prealbumin. We found a decrease in CRP, SAA and orosomucoid levels after 60 days of β-glucan treatment. Glucan not only suppressed inflammatory manifestations, but also improved patient's conditions.

Keywords: Glucan; Inflammation; Cancer; Fatigue; CRP

Introduction

Immune-mediated inflammatory diseases (IMIDs) represent a group of chronic and particularly exhausting diseases, which include disproportinate and excessive reactions, either caused or mediated by deregulation of cytokines and subsequent acute or chronic inflammation. IMIDs include Crohn disease, ulcerative colitis, psoriasis, rheumatoid arthritis and systemic lupus erythematosus. Prevalence of these diseases is rather high and involves 5-7% of the population in developed countries. The need to constantly monitor the immune reactions of these patients is based on the high risk of development of cancer [1-4].

Reports describing the effects of stress on the immune system are of high interest for not only scientists and clinicians, but also experts in psychoneuroimmunology. It is well established that psychological stress can reduce or disregulate immune reactions both via hypothalamus-pituitory-adrenal (HPA) axis or via sympatetic-adrenal-medular axis. Neuroendocrine hormones released from the thyroid gland stimulate immune cells to produce high levels of IL-1 which subsequently induces increased production of corticotropin-releasing hormone by hypothalamus. This is followed by release of adrenocorticotropic hormone ACTH and corticosterone by the anterior pituitary and suprarenal glands. These stress hormones may result in deregulation or supression of immune responses. Reduction of NK cell activity and lower IFN production will result in lower control of latent herpes viruses expression with acute inflammatory response. Besides physiological stressors, the physical stressors can play the same role [5].

Stress can cause syndromes and a subsequent diagnosis of chronic fatigue syndrome. Patients coming to our Department are quite often diagnosed with this problem. However, the majority of these patients are, after detailed evaluation and after using full criteria for diagnosis of chronic fatigue syndrome, moved into different diagnoses. These new diagnoses are often related to fatigue indicationssuch as depressions, anxiety, neurastenia, fibromyalgia, hypothyreoidism, asthma bronchiale or Lyme disease. Careful definition of disease using CDS or Oxford criteria [6,7] allows (at least partially) a decision on diagnosis, but the precise definition is not possible. Persistant fatigue without significant clinical manifestation often remains major display, allowing diagnosis of idiopatic chronic fatigue. Indecision in diagnosis is increased by information based on evaluation of chronic fatigue syndrome of Gulf War veterans [8,9].

Fatigue is the most common syndrome accompanying cancer diseases and their treatment. Basically 100% of cancer patients describe fatigue during treatment and more than 50% describe these problems lasting for more than 12 months after the end of treatment. In all these cases, the intensity of these syndromes qualify the description "cancer-related fatigue" (CRF). In cancer patients, fatigue is not only a manifestation of treatment, but also reflects biological effects of the tumor. Despite the fact that some mechanisms leading to CRF are elucidated, we still do not know all of them. CRF represents a multifactorial process involving numerous physiological and psychosocial factors [10]. Persisting fatiguecan be connected with immune processes, most of all T-cell inflammatory response or TNF, interferon [10] or IL-6 release [11]. Activation of these mediators can be influenced by several additional impacts such as psychosocial or comorbidity (such as anemia, malnutrition, infection, or mineral deficit), influences of treatment or others. The combination of these influences, particularly endocrinic, hematological, metabolical and

detoxification strain, is connected with the acute inflammatory response. This response is manifested not only by changes in concentration of numerous plasma proteins (acute phase proteins), but also by extensive changes of physiological, biochemical and nutritional conditions [12]. The number of proteins involved in response to inflammation is vast and includes not only proteins with significant increase, but also proteins which production is suppressed [13-16]. Numerous studies found relation between CRF and levels of CRP [17] or serum amyloid [18]. Progress in our understanding of the neurobiological mechanisms responsible for CRF is necessary for the development of adequate treatments [19].

β-Glucans (subsequently named glucan) are well-established modulators and activators of various biological and immunological activities including regulation of phagocytosis, cytokine synthesis and release, antibody formation, anti-cancer reaction and stimulation of intracellular signaling [20-23] and currently represent the most studied natural immunomodulators. Glucan alone or in combination with various molecules such as vitamin C and resveratrol [24], humic acid [25] or selenium [26] has positive effects on complex treatment of cancers and most of all on clinical manifestations persisting after cancer [23].

Our previous clinical studies showed that even a short term supplementation with glucan resulted in significant improvements of mucosal immunity [21,27]. In addition,glucan has been found to ameliorate both experimentally- or physically-induced stress [28,29]. Recently, glucan was implicated to attenuate chronic fatique syndrome [30]. These studies led us to hypothesize that adding glucan to the diet might have anti-inflammatory effects and improve clinical signs of CRF. Therefore we decided to evaluate the potential effects of glucan supplementation on CRF and to elucidate the relation between the level of various potential inflammatory biomarkers for fatique and glucan supplementation.

Materials and Methods

Protocol

A randomized, double-blind, placebo-controlled trial compared β-glucan #300 and placebo in patients followed up in patients at the end of complex treatment of cancer disease. We evaluated 58 patients. At the end of the study, we evaluated 26 patients in the placebo-supplemented group with an average age 59.9±9.8 years, and 32 patients (24 females and 8 males) in the glucan-supplemented group with an average age 59.3±10.2 years. In all individuals we diagnosed chronic fatigue syndrome based on International Case Definition criteria with Cancer Related Fatigue criteria. All patients were tested for comorbid health state, possible effects of medical treatment, and psychological factors such as depression and anxiety. In addition, blood was collected at the beginning and at the end of the study. Subjects were randomly assigned to groups which were blinded to intervention. During the intervention period, the subjects consumed 200 mg/d of β-glucan or placebo for 60 days. Both glucan and placebo capsules looked identical. Subjects were routinely evaluated by the medical staff.

This study was performed in agreement with the Helsinki declaration (revised version 2000.09.01) and in full compliance with the rules for clinical testing for the Czech Republic. All patients were fully informed about the goals of the study and their consent was given in all cases.

Tests

In tested samples we measured the concentrations of CRP, serum amyloid, orosomucoid and prealbumin. We used nephelometer Siemens BM II as suggested by the manufacturer. All necessary diagnostics and control kits were used from the same manufacturer.

Glucan

Yeast-derived insoluble glucan #300 was purchased from Transfer Point (Columbia, SC, USA). This glucan is over 85% pure. A single daily dose of 200 mg was used for 60 days.

Statistical analysis

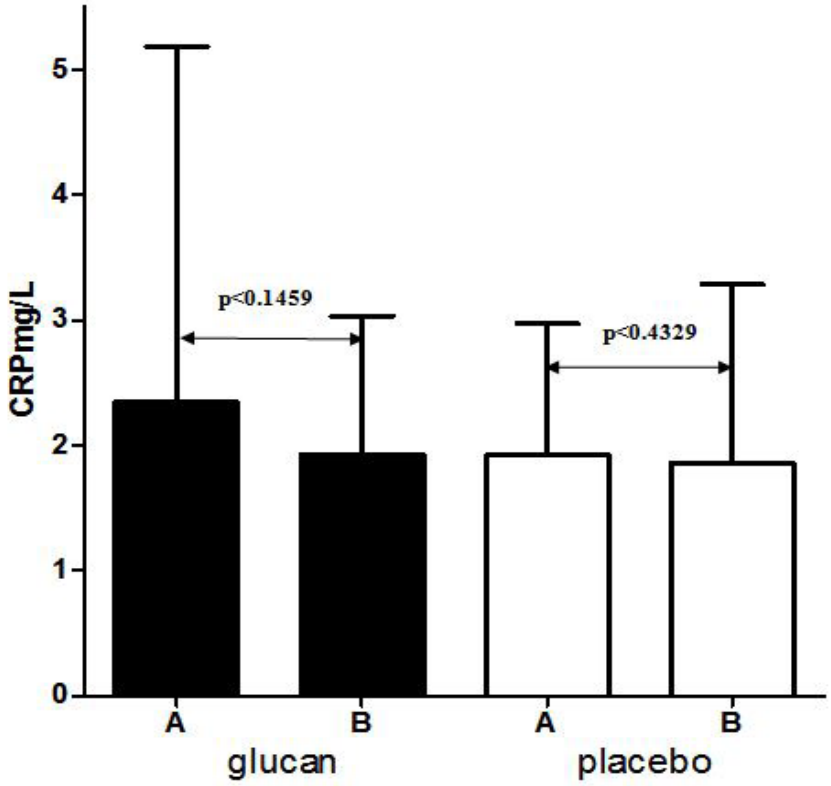
Statistical significance was evaluated by a Wilcoxon paired t-test using a GraphPad Prism 5.04 software (GraphPad Software, USA). Statistical significance between individual groups used a $P < 0.05$ level. The results represent mean and SD. Assumption that the differences are sampled from a Gaussian distribution was tested using the Kolmogorov-Smirnov distance test.

Results

Figure 1 summarizes levels of CRP. In the glucan-supplemented group, the level at the beginning of study was 2.34±2.84 mg/ml, glucan caused decrease to the 1.92±1.11 mg/ml. In the placebo group, the decrease was less profound (from 1.92±1.05 mg/ml to 1.86±1.42 mg/ml).

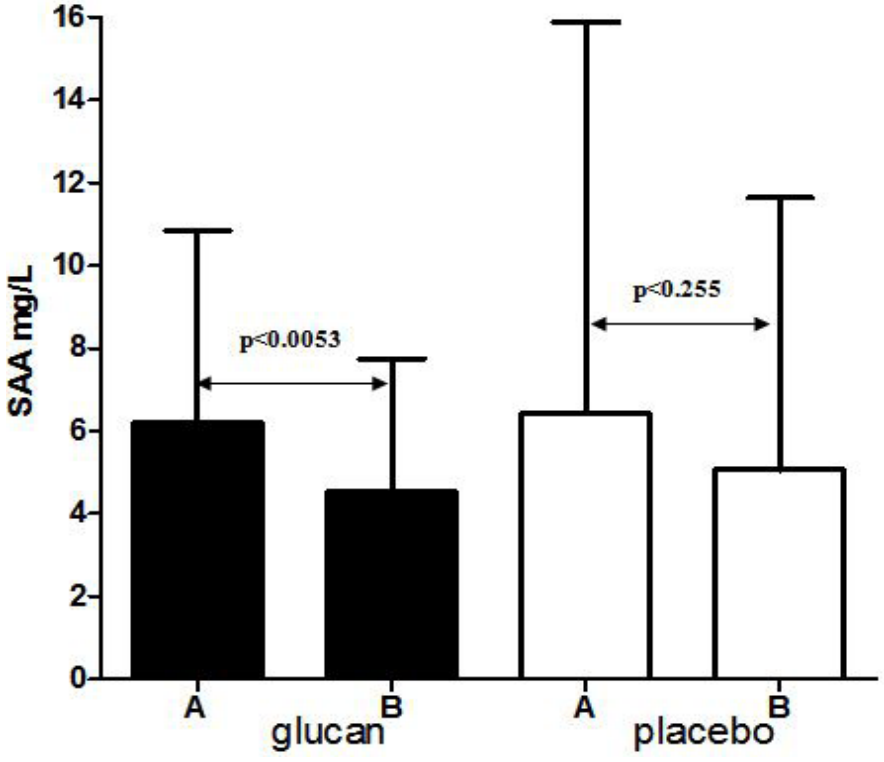
In the case of serum amyloid (Figure 2), we found a significant reduction of the level from 6.18±4.65 mg/ml to 4.51±3.24 mg/ml, whereas the placebo group showed an insignificant decrease from 6.41±9.49 mg/ml to 5.05±4.59 mg/ml.

Levels of orosomucoid in the glucan-treated group were 0.86±0.17 mg/ml and were significantly reduced to 0.81±0.17 mg/ml (Figure 3). In placebo groups, no differences were found (0.86±0.24 mg/ml vs. 0.86±0.21 mg/ml).



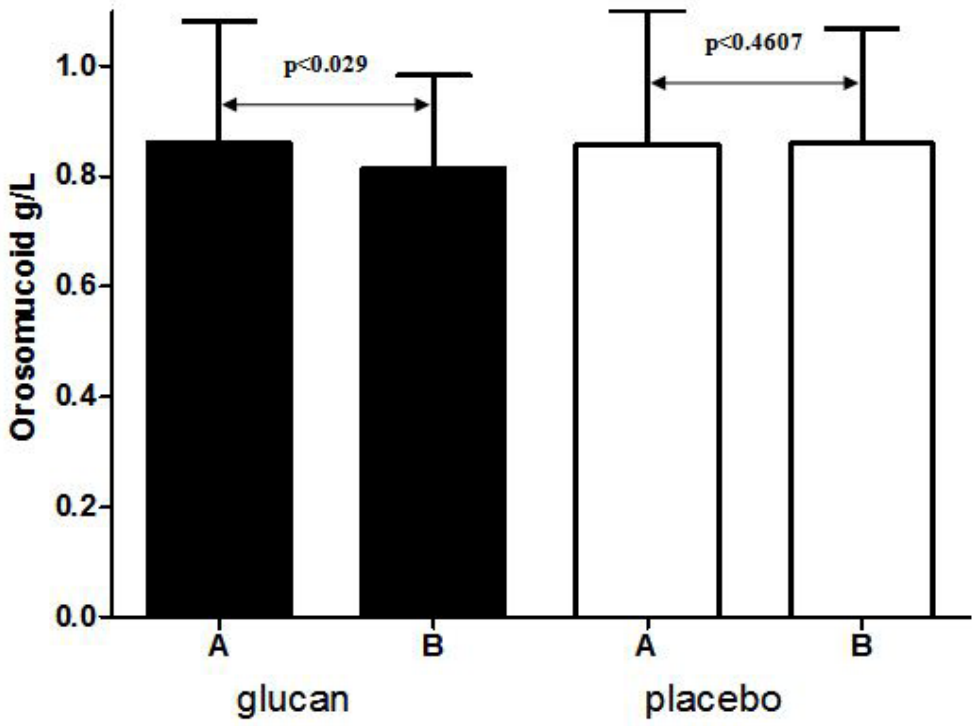
Results are given as mean ±SD

Figure 1: Effects of glucan on levels of C-reactive protein
(A) Before therapy
(B) After therapy



Results are given as mean ±SD

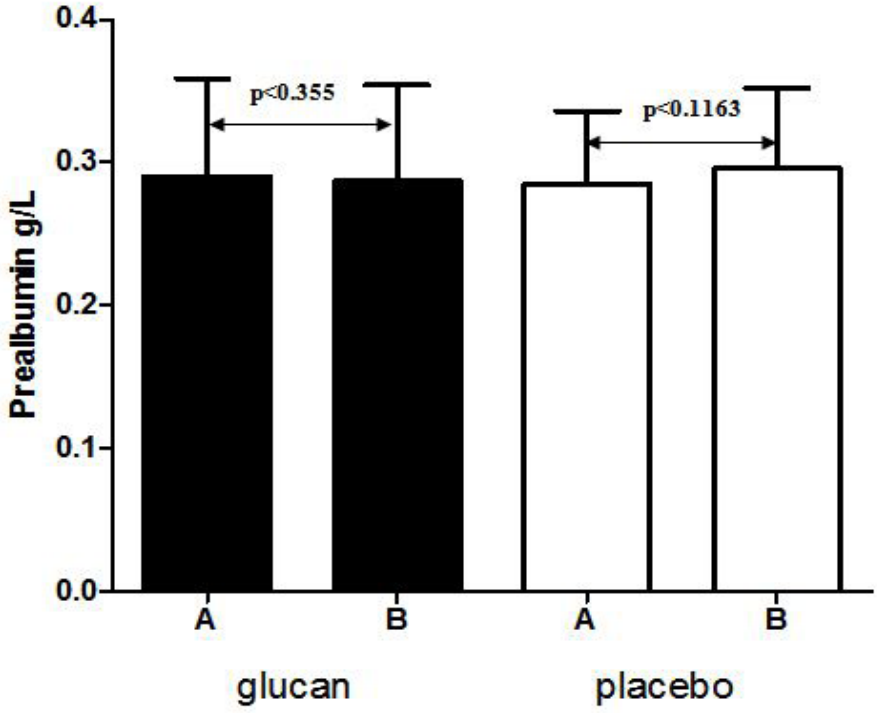
Figure 2: Effects of glucan on levels of serum amyloid A (SAA)
(A) Before therapy
(B) After therapy



Results are given as mean ±SD
Figure 3: Effects of glucan on levels α 1 – acid glycoprotein (orosomucoid)
(A) Before therapy
(B) After therapy

In the case of prealbumin, no statistically-significant changes were found in either group (Figure 4). In the glucan group, the levels of prealbumin were 0.29±0.60 mg/ml at the beginning of the study and 0.29±0.67 mg/ml at the end, in the placebo group it was 0.29±0.05 mg/ml and 0.29±0.06 mg/ml).

In addition, patients filled the questionnaire and the possible exclusion was based on previous studies [31,32].



Results are given as mean ±SD
Figure 4: Effect of glucan on levels prealbumin
(A)Before therapy
(B) After therapy

Discussion

Despite decades of research, chronic fatigue syndrome (CFS) remains a serious disorder of unknown etiology, characterized by the major manifestation of profound fatigue. The complexity of this syndrome together with problems in diagnosis and studies induce the need for extensive, systemic and integrated approach, both for classification and evaluation of additional causes of fatigue. It is necessary to perform a complex evaluation of causes and definition in all patients with fatigue lasting longer than 30 days. Fukunda, et al. [6] described several states explaining chronic fatigue which should be considered in differential diagnosis of CFS. It is impossible to define several of these factors by laboratory tests (e.g., fibromyalgia, depression, neurastenia and others), the others can easily be confirmed (allergy, asthma, hypothyroidism). In addition, we cannot overlook some infectious diseases with display of fatigue, (e.g., Lyme disease or syphilis), autoimmune diseases and other health problems [5,7,33]. Major criteria for classification defining CFS are well documented in literature [5,6]. In addition, CFS was studied in a full laboratory and clinical setting in Gulf War veterans [8,9]. Based on classifications described by [6], many of these patients showed numerous clinical signs of CFS. These studies led us to our work involving diagnosis of CFS which is connected with cancer disease. We focused on patients treated for cancer in time interval after more than 3 months after the end of complex surgery, radiation and/or chemotherapeutic treatments. Out of numerous possible causes of CFS [10] we focused our attention on questions of comorbid conditions resulting from medical treatment, particularly from stress-related depression of immune reaction and anemia. Particular attention was focused on the diagnosis of conditions able to activate both acute and chronic infections.

Sedimentation is lately used less for diagnosis of inflammatory reaction and this technique is replaced by measurements of C-reactive protein (CRP) or other positive or negative proteins of the acute phase. A summary of these proteins is reviewed by Gabay and Kushner [3], including a description of their induction by cytokines and other molecules. Many of these proteins are multifunctional and in various stages can influence either activation or reduction of inflammation. However, clinical practice uses only a very limited amount of these indicators. The reason is based on technical conditions, need for proper standardization of results, their biological importance and total costs. Based on these criteria, evaluation of CRP is currently the most common. This peptide is able to bind phosphocholin and subsequently recognize some pathogenic organisms as well as phospholipid components of damaged cells. In addition, CRP can support phagocytosis by complement activation, helping to eliminate target cells. Another important anti-inflammatory effect of CRP includes is its ability to induce production of inflammatory cytokines and monocyte-derived factors.

Another protein signalling inflammation is serum amyloid A (SAA). This protein is a member of apolipoproteins, and is able to fast bind to high-density lipoprotein and to affect cholesterol metabolism. The result is adhesion and chemotaxis of phagocytes and lymphocytes. Induction of SAA is increased by corticoides [3,34]. SAA is probably involved in pathogenesis of some chronic inflammatory diseases. Dynamics of CRP and SAA expression are in good correlation with the higher range of response found in case of SAA [13]. From the protein with negative effects, the most important one seems to be prealbumin which can serve as an important indicator of both inflammation and nutritional state. Some observations of the prealbumin levels suggest the importance of careful monitoring of individual patients as the graduate increase in prealbumin levels signals of adjustments of metabolic and nutritional state [35].

Orosomucoid (alpha-1-glycoprotein) is common in human plasma at a concentration between 0.5 to 1 mg/ml. During inflammation we can first observe changes in levels of CRP and SAA followed by an up to fivefold increase of orosomucoid levels. IL-1 and hepatocyte-produced IL-6 are the most common inducers of orosomucoid. This molecule can bind bacterial endotoxins and protect against endotoxin-induced septic and hypovolemic shock. Anti-inflammatory action of orosomucoid includes inhibition of neutrophil activation and modulation of lymphocyte response. In addition, some studies found antiapoptotic effects. Orosomucoid serves as a transport protein with the ability to transfer endogenous aterogenic lipids, regulate immune responses and homeostasis [3,4,15].

Prealbumin belongs to the groups of negative proteins of acute inflammation. A decrease in its values, together with other members of this group (such as serum zinc, iron, albulin, transferrin and others) results in temporary availability of free hormones which usually bind to these molecules. This negative inflammatory response is sometimes described as acute booster reaction [3,4,15,35].

Therapy of CFS is extremely difficult. It is based on quality knowledge of full medical conditions of patients, both their psychological and physical conditions. It uses not only nonpharmacological approaches (such as excercise or psychological interventions), but also psychostimulating and empirical support [10]. In our study, we focused on how to influence immunological mechanisms, which are damaged not only by the disease and its treatment, but also by posttherapeutic persistent conditions. Expression of inflammation and immunity-mediated inflammatory diseases can result in inadequate and excessive immune response with cytokine disregulation and induction of acute or chronic immune reaction. These reactions can induce both pro- and anti-tumorigennic effects, which subsequently can persist and become inducer of progression or regression of cancer disease [1].

Based on our experience of glucan action confirmed by several clinical trials [20-23], we decided to influence mechanisms of nonspecific immunity by glucan supplementation. Glucans are well-documented natural modulators having significant biological and anti-cancer effects. In addition, glucans can stimulate phagocytic activity, production of cytokines and numerous other immune mechanisms involed in the suppression of cancer development [23,36]. Additional studies showed that glucan increased

sponteneous regression of low grade cytologic irregularities [37]. Monitoring of health conditions often uses various proteins, as it brings valuable information about actual nutritional background and about possible inflammatory response. The importance of evaluation of both positive and negative proteins of acute inflammatory response is increasing in their mutual combination (Acute Phase Index API and/or Nutritional and Acute Phase Indicator NAPI). These indexes can be used as prognostic indicators of inflammation and/or nutrition [15].

Several proteins of acute phase can influence one or more steps leading to inflammation. The main role of CRP is the ability to bind phosphocholin and to recognize foreign pathogens and phospholipid components of damaged cells. CRP activates complement and via binding to the phagocytozing cells initiates elimination of targets by interaction with both humoral and cellular effector systems of inflammation. In our groups of patients we found no changes in CRP levels in the three months after the end of the basic treatment time period. Glucan supplementation had no effects on CRP levels. This finding corresponds with the fact that the dynamic of a CRP decrease is the fastest of all markers of inflammation and gives us the information that posttherapeutic inflammatory manifestations were eliminated.

Serum amyloid (SAA) belongs to the main indicators of primary acute inflammatory reaction, but its physiological functions remain unclear [4]. It is known that SAA induces adhesion and chemotaxis of phagocytosing cells and lymphocytes and induces cytokine production and secretion of metaloproteinase. It might be involved in the pathogenesis of chronic inflammatory diseases [34]. SAA inhibits lymphocytes and it seems that its anti-inflammatory effects are more selective than systemic. Significant decrease of SAA levels compared to slight descrease in placebo group demonstrates the positive role of glucan in cancer patients. Variable changes of tested proteins (CRP, SAA) show that individual parts of acute inflammation are regulated separately [4]. This is in agreement with our findings and it supports the fact that it is not optimal to evaluate only one parameter of inflammation. Focusing on only one factor we will not get full and exhausting information about the actual health state.

Orosomucoid has protective and anti-inflammatory effects, including the ability to inhibit neutrophil activation and to modulate lymphocyte response. In addition, anti-apoptotic effects have been described [4]. Slight increase in orosomucoid levels in our patients is longer (when compared to CRP and SAA levels) and suggest persistant inflammation [2]. Strong and significant suppression of orosomucoid levels in the glucan-supplemented group demonstrates the substantial anti-inflammatory role of glucan.

One of the negative proteins of acute inflammatory reaction is prealbumin. We found no significant changes in prealbumin levels in either the glucan-supplemented group or in the placebo group. Prealbumin levels are normal, reveal solid nutritional reconvalescence [35] and correspond with the regulation of metabolic and nutritional situations of our patients. In addition, these findings suggest a reduced risk of increased length of stay (LOS).

Conclusion

In conclusion, our report found that supplementation with glucan offers positive effects on the health situation of patients after cancer. Glucan not only suppressed inflammatory manifestations, but also improved the patient's conditions.

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