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THE EVALUATION OF VITAMIN C SUPPLEMENTATION ON NUTRITIONAL STATUS OF PATIENTS WITH ACUTE MYELOID LEUKEMIA UNDERGOING CHEMOTHERAPY

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Keywords:

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ABSTRACT: Background: Leukemia is the seventh common cancer in Iran, and AML is considered as the most common type. Malnutrition is common among patients with cancer. Vitamin C deficiency has a high prevalence among patients with cancer, which may influence a patient's survival chance. This study was aimed to evaluate the effect of vitamin C supplementation on nutritional status and serum albumin in patients with acute myeloid leukemia referred to Shariati Hospital in Tehran. **Methods:** This study was recruited by a randomized selection of 50 patients with AML, including entrance criteria, into 2 groups including the supplement group and control group. The duration of the study was 1 month. Nutritional status was assessed by the PG-SGA questionnaire, body weight, serum albumin status, and 3 days of food record before and at the end of the study. **Results:** The results of this study have shown that the nutritional status and body weight in the supplementation group have improved significantly (p-value=0.001 and 0.004, respectively). The serum albumin status has increased significantly in the supplementation group compared to the control group. (P-value=0.002). **Conclusion:** The results of this study have suggested that vitamin C supplementation in patients with AML under chemotherapy has improved nutritional status and reduced malnutrition due to chemotherapy side effects.

INTRODUCTION: Leukemia is the seventh common cancer in Iran and AML is considered as the most common type of leukemia [1, 2, 3]. It is estimated that the incidence of ALM is 3/6 per 10000.

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ALM is a condition in which the bone marrow myelocyte cells stop growing at the first stage, which leads to more immature cells and reduction in natural cells count. Fatigue, nausea, and appetite loss are common symptoms of ALM. Patients with ALM are prone to malnutrition and weight loss which may decrease the chance for treatment [1].

Nutritional adequacy is crucial for body mechanisms [2, 4] and immune system optimal health and malnutrition may lead to poor quality of life in these patients [5]. Neutropenic diet is a suggested dietary pattern for infection prevention [6] but there

are still contradictory results about its efficacy [4-12]. The studies have suggested that raw and cooked diet have no effect on the infection incidence [4-16] and patients who adhere from the cooked dietary pattern, the principal of neutropenic diet, have significantly lower vitamin C intake (38.9%). Moreover, the level of vitamin C decreases in blood malignancies [17]. Vitamin C is a water-soluble vitamin with antioxidant properties due to its tendency in losing electrons to 8 crucial enzymes involving in neutralizing free radicals [18].

Oxidative stress prevention and increasing in anti-oxidant capacity will affect various health-related and healing processes in the body, including cell aging, inflammation reduction, and cancer-related mechanisms, so human body physiologic mechanisms seem to be a key component in diseases overcoming [18, 19, 20, 21]. Studies have suggested that oral intake of vitamin C can reduce CRP and IL-6 [18, 22] and even reinforce the immune system. Vitamin C interacts with inflammatory cytokines and protects immune system cells from ROS. Moreover, ascorbic acid derivatives may lead to more antibodies production [23, 24]. The aim of this study was to examine the impact of vitamin C supplementation along with a neutropenic diet on nutritional status and serum albumin level in patients with ALM undergoing chemotherapy.

MATERIALS AND METHODS: This randomized controlled clinical trial was conducted for a period of one month. 50 Patients diagnosed with ALM referring to Shariati Hospital Oncology Department in Tehran were selected for this study according to the formula below and then divided into "study" and "control" groups randomly.

$\mu_1 - \mu_2 = 4$
$s1 = s2 = 5$
$\beta = 20\%$
$\alpha = 0/05$
$Z_{1-\alpha/2} = 1/96$
$Z_{1-\beta} = 0/84$

$$n = \frac{\left(z_1 - \frac{\alpha}{2} + z_1 - \beta\right)^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)}$$

Inclusion Criteria for the Study:

- Willingness to participation.
- Age older than 18 years.
- AML diagnosis approved by hematologist,
- A maximum of one month from the onset of a person's illness,
- Simultaneous chemotherapy protocol,
- Affected by any type of AML except type 3.

Exclusion Criteria for the Study:

- Any vitamin-mineral supplement consumption,
- BMI<18/5 before entering the study,
- History of chemotherapy drugs consumption,
- bone marrow transplant,
- Pregnant and lactating women.

Energy Calculation and Dietary Suggestions: The total required energy was calculated by Mifflin formula according to body weight and height, appropriate stress factor and physical activity (1.36 according to previous studies). The diet pattern included 50-55% of carbohydrate, 15-20% protein, and 30% fat.

The nutritional suggestions were given as brochures and included: the consumption of cooked vegetables, raw banana and pilled orange, fruit compote and juices, well-cooked egg and meat, pasteurized dairy products and boiled water. All patients were advised to avoid consuming raw vegetables [7, 10]. Each patient was given 28 fizzy tablets containing 500 mg vitamin C for the duration of 4 weeks produced by Vita Fiz company approved by the FDA.

Anthropometric Measurements: The patient's body weight and height were measured by seca scale and height gauge with the precise of 100 grams and 0.5 centimeters, respectively. The body mass index was calculated using weight and height.

Vitamin C Assessment and Calorie Intake: For energy and vitamin C intake assessment, 3 days food records were taken before and at the end of the study via interview and the data were analyzed by nutritionist 4 software.

Malnutrition Severity Assessment: The severity of malnutrition was assessed by PG-SGA malnutrition evaluation questionnaire which included weight loss, any changes in food intake,

and any complaints related to nutrition, physical activity status and physical examination for patients with cancer undergoing chemotherapy. The percentage of weight loss was calculated according to questionnaire manual, past and current body weight in the past first and 6 months. After submitting the data from the clinical examination, the scores were ranked in each part. For nutritional complaint and adipose tissue examination, >6 was severe, 3-6 was moderate and <3 was low. For weight loss during the past 6 months, the ranking was >20%, 10-20%. 5-10% and<5% and for muscular adipose tissue loss were >6 for severe, 4-6 for moderate and <3 for low which was explained according to required intervention for questionnaire and malnutrition severity including level A (appropriate nutrition), B (at risk of malnutrition) and C (severe malnutrition).

Serum Albumin Assessment: Blood samples were collected before and after the chemotherapy and serum albumin was measured after centrifuging and serum separation in -80°C with coloring method using Zell bio Germany kit with the accuracy of 0.2 gr/dl.

Statistical Analysis: All of the data was analyzed by SPSS software version 21. The means of the two groups were compared using paired t-test in the case of normal distribution.

RESULTS: Of the 58 subjects recruited in the study, two subjects dropped out and six subject was excluded because of a lack of consumption supplement. There was no significant difference in gender, age, and height at the first of the study between the two groups **Table 1**. The average age was 40.80 ± 12.77 and 38.36 ± 13.75 for supplementation and control group, respectively. There was no significant difference between energy, carbohydrate, protein, fat, vitamin E and vitamin C intake at the beginning and the end of the study in each group. As shown in the table, the average of energy, protein, fat, vitamin C and E intake between the two groups showed a significant difference at the end of the study **Table 2**.

TABLE 1: INTERVENTION AND CONTROL GROUPS PARTICIPANT'S GENERAL INFORMATION

Variable	Intervention group	Control group	P-value**
Height (Cm)	171.22±171.09	169.60±8.95	0.56
Age (year)	40.80±12.77	38.36±13.75	0.51
Gender			
Male	14	15	0.7
female	11	10	

Age and height are reported as standard deviation average,**t-test

TABLE 2: CALORIE AND SOME OF THE NUTRIENTS INTAKE IN PARTICIPANTS

Variable	Baseline	At the end	P value**
Energy			
Intervention group	1435.82±337.81	1556.73±352.33	0.15
Control group	1374.95±410.88	1270.22±389.49	0.33
P value***	0.12	0.004	
Protein			
Intervention group	71.47±25.95	80.69±24.99	0.58
Control group	66.29±19.14	64.82±55.52	0.20
P value	0.12	0.02	
Carbohydrate			
Intervention group	202.93±53.20	225.43±52.01	0.08
Control group	179.19±19	176.86±58.72	0.91
P value	0.17	0.003	
Total fat			
Intervention group	36.76±9.72	38.92±10.59	0.38
Control group	35.26±11.15	33.46±9.70	0.29
P value	0.20	0.06	
Vitamin C			
Intervention group	205.01±106.68	224.14±62.27	0.29
Control group	216.13±125.01	177.90±74.89	0.14
P value	0.73	0.02	
Vitamin E			
Intervention group	3.26±1.14	3.12±0.76	0.55
Control group	2.43±1.09	2.55±0.93	0.68
P value	0.14	0.02	

*variable are reported as average ± standard deviation, *** paired t-test, *** t-test

The results have suggested that there were no significant differences in serum albumin level between the two groups at the beginning of the study. The serum albumin level increased in the intervention group (from 3.45 ± 0.63 to 3.59 ± 0.57). But it was not significant. Serum albumin decreased significantly in control group (from 3.51 ± 0.79 to 3.09 ± 0.5) at the end of the study (p-value= 0.03) **Table 3**. There was no significant difference between body weight, body mass index at the beginning and the end of the study between the two groups **Table 4**. The nutritional status was not significantly different at the first bud has shown a significant difference at the end of the study between the two groups (p-value=0.001) **Table 4**.

TABLE 3: PARTICIPANT'S SERUM ALBUMIN LEVEL COMPARISON AT THE BEGINNING AND THE END OF THE STUDY

Variable	Baseline	At the end	P-value**
Albumin			
Intervention group	3.45±0.63	3.59±0.57	0.33
Control group	3.51±0.79	3.09±0.5	0.03
P value***	0.75	0.002	

*variable are reported as average ± standard deviation, *** paired t-test, ***t-test

TABLE 4: PARTICIPANT'S BODY WEIGHT, BODY MASS INDEX AND NUTRITIONAL STATUS AT THE BEGINNING OF THE STUDY COMPARED TO THE END OF THE STUDY*

Variable	Baseline	At the end	P-value**
Weight			
Intervention group	74.38±14.93	75.46±14.34	0.14
Control group	74.87±11.94	71.38±12.64	0.13
P value***	0.89	0.29	
Body mass index			
Intervention group	25.32±4.41	25.72±4.2	0.14
Control group	26.21±5	24.92±4.76	0.12
P value	0.51	0.53	
Nutritional status			
Intervention group			
Proper nutrition	7	19	
Prone to malnutrition	12	6	
Severe malnutrition	6	0	
Control group			
Proper nutrition	5	1	
Prone to malnutrition	10	6	
Severe malnutrition	10	18	
P value****	0.46	0.001	

*variable are reported as average ± standard deviation, **paired t-test, ***t-test, ****Chi Square

DISCUSSION: Vitamin C deficiency is common among patients with cancer and it is estimated that 30% of patients with advanced cancer are vitamin C deficient which may affect their chance for survival and even cause some clinical problem such as fatigue, anorexia, and depression. This deficiency may be as a result of nausea and vomiting as a side effect of cancer and may increase the risk of unbalanced diets. The studies have indicated that there is a significant association between vitamin C status and serum albumin level. Moreover, malnutrition as a cause of chemotherapy, may lead to malnutrition and increase the risk of vitamin C deficiency in patients with cancer [1, 2, 25].

On the other hand, infection is another common problem in patients with AML and patients with cancer undergoing chemotherapy, which may be caused by disease or treatment processes. So interventions for decreasing the risk of infections, such as neutropenic diets are usually used in order to decrease the exposure to infectious agents. Karen Moody and et al have suggested that neutropenia is a clinical side effect of chemotherapy in patients with cancer and the decrease in the number of neutrophils may increase the risk of infections [26, 27].

In this study, vitamin C supplementation combined with neutropenic diet were given to AML patients for the first time in Iran. As mentioned before, neutropenic diet is a common diet among patients with leukemia under chemotherapy including cooked foods and vegetables, raw banana and pilled orange, fruit compote and juice, well-cooked meat and egg, pasteurized dairy products, boiled water and avoiding from salad and raw vegetables consumption, which includes safety points in preparation of the foods, also [14, 18, 25, 28-32].

Vitamin C loss during cooking is approved by the previous studies. This study was aimed to assess the effect of neutropenic diet on nutritional status, serum albumin level and anthropometric factors in AML patients under chemotherapy. The results have suggested that vitamin C supplementation has improved nutritional status in these patients. The rate of patients prone to malnutrition and severe malnutrition has decreased by 48%. In a study on 63 patients with leukemia in 3 hospitals of Tehran, 19.4% of patients were malnourished before the chemotherapy and after that, 76.1% had moderate malnourished and 6.3% were severely malnourished. Khoshnevis and *et al.*, have suggested that 53.1% of their study subjects were malnourished. Among these patients, 29.1% were moderately malnourished and 24% were severed malnourished [29]. So the results suggest that malnutrition is common among patients with cancer under chemotherapy which is compatible with our results.

The analysis of 3 days food records have suggested that the average of energy, protein, and fat intake in the intervention group were significantly different compared to the control group at the end of the study. There was no significant difference between vitamin E and C intake in the two groups at first, but there was a significant difference in the intervention group compared to the control group at the end of the study. At the end of the study, the intake of macronutrients (carbohydrate. Protein and fat) and micronutrients (Vitamin C and E) have significant differences in the intervention group compared to the control group.

There were no significant differences between body weight and body mass index in the two groups. Albumin is an indicator for malnutrition which has significantly increased in the intervention group at the end of the study. Fumeron and *et al.*, aimed to evaluate the effect of vitamin C supplement on inflammatory factors and oxidative stress in hemodialysis patients and have suggested that the serum albumin level has increased in the patients under hemodialysis but was not significant compared to the control group [18, 19, 28]. Quan Jun Yang and *et al.*, have suggested that cancer cachexia is characterized by weight loss, adipose tissue wasting, muscle atrophy and loss of appetite. Serum albumin levels and some other factors such as IGF-1 are considered as cachexia side effects during cancer which may be due to low carnosine depeptidase-1 level in patients with gastrointestinal cancer [33, 34, 35, 36, 37].

Daniel W. Nixon *et al.,* also realized that the serum vitamin C, vitamin A, and folate are lower in 20-45% of patients in the second phase of their study and have concluded that protein and energy undernutrition in common in patients with cancer and is combined with the loss of adipose tissue and visceral protein. Furthermore, they have assessed the degree of malnutrition with creatinine to height ratio and serum albumin level. The results have suggested that the lower serum albumin level (lower than 3.5 g/dl) is significantly related to survival incidence [25].

CONCLUSION: According to the results, it can be concluded that vitamin C supplementation in a patient undergoing chemotherapy significantly improves nutritional status. Also, food intake and serum albumin are improved by vitamin C supplementation. Further studies are needed to approve the results of the present study.

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COMPLIANCE WITH ETHICS GUIDELINE: Study protocol was approved by the Nutrition Research Institute ethical committee. All participants gave their written informed consent before they participated in the study.

COMPETING INTEREST: The authors declare that they have no competing interests.

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