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ORIGINAL ARTICLE

L-Carnitine, L-propionyl carnitine and malndialdehyde levels of pediatric patients with solid tumor

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Abstract:

It is known that the production of free O_2 radicals and oxidation products have a significant increase in patients with cancer. There are endogeneous protection systems in order to remove free O_2 radicals. One of these endogeneous protection system is carnitine. Carnitine has an important role in muscle functions and in obtaining energy from the membranes of body cells.

This study aims to investigate the role of L-carnitine, L-propionyl carnitine and malondialdehyde (MDA) in antioxidant mechanism in children recently diagnosed with solid tumor. The study group were consisted from 57 children from 2 children's cancer centers (Gazi University Pediatrics Department and Sami Ulus Pediatrics Hospital) who were recently diagnosed with solid tumor and 45 healthy control. There was no significant difference in free carnitine and L-propionyl carnitine levels between patients with solid tumor and healthy controls. But, MDA levels were significantly higher in children with recently diagnosed solid tumor than in healthy controls.

Keywords: *Solid tumor, L-carnitine, L-propionyl carnitine, malondialdehyde (MDA)*

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Introduction

Carnitine which is taken with diet is is a micronutrient and an amine, produced from methionine and lysine in liver and kidney. It provides beta oxidation of long chained fatty acids [1,2,3]. Fatty acid metabolism is a major source of muscular energy and deficiencies in carnitine are manifested as low energy levels and muscular weakness. It enables taking away of toxic carnitine esters and other metabolites from mitochondria [4]. Primary or secondary carnitine deficiency can occur. Primary deficiency is defined as the genetic defects in the biosynthesis or in the transfer of carnitine. Carnitine homeostasis is maintained by absorption, sythesis and renal reabsorption. Chronic hemodialysis, diabetes mellitus, prematurity, gastrointestinal malabsorption, liver disease, organic acidemies, fatty acid oxidation defects, antiepileptic drugs such as valproic acid, malignancy and malnutrition are the main causes of secondary carnitine deficiency [2,5].

L-propionyl carnitine is formed by the esterification of L-carnitine with propionyl [6]. It suppresses the production of

hydroxyl radicals. It is shown that L-propionyl carnitine is an antioxidant which has affects as binding superoxide radicals that cause DNA damages induced by hydrogen peroxide (H_2O_2). Since it is more lipophilic compared with L-carnitine, and it is more effective in absorption of fatty acids in cardiac cells [1,4,7].

MDA; is the main oxidation product of peroxidation of multiple unsaturated fatty acids which has a biological importance. MDA, a dialdehyde formed at the time of lipid peroxidation, can cause metabolic deficiencies, cell damages and even death unless it is taken away from the environment [8,9,10]. It is known that the production of free O_2 radicals and oxidation products has a significant increase in children with cancer [11]. At the time of the diagnosis, multiple oxidant agents such as H_2O_2 are produced by tumor cells and as the illness accelerates, oxidative stress continues. Both chemotherapy and malignity increase lipid peroxidation products in cancer patients. There are endogeneous protection systems in order to remove free O_2 radicals. One of protection system is carnitine [3,12]. L-propionyl carnitine prevents endothelial damages by hindering the production of free radicals which are likely to increase in cancer patients [6,13].

Malnutrition frequently occurs in children who have cancer. The causes of malnutrition are as follows;

1-) In cancer patients, some metabolic changes in carbohydrate and protein metabolism occur. Plasma concentrations of free fatty acids, lipid distribution, abnormalities in peptid synthesis can ocur as a result of consumption of body nutrients by tumoral cells

2-) Catabolism increases with the effect of malignity.

3-) Chemotherapy which is applied to most of the patients with cancer have negative effects in nutritional status of these patients. If the intake of carnitine with the diet is insufficient in cancer patients, carnitine deficiency will occur. Because sufficient levels of carnitine could not be protected in body reserves [14,15,16,17].

To our knowledge, no studies exist that evaluate plasma L-carnitine, L-propionyl carnitine and MDA levels in newly diagnosed cancer patients.

Materials and Methods

This study has been done among cancer patients treated at Gazi University Medical Faculty, Department of Pediatrics and Dr.Sami Ulus Children's Hospital, who were not received chemotheraphy or radiotheraphy yet. A total of 102 children, 57 with solid tumors and 45 healthy controls between 1 and 17 years of age were enrolled in this study. Family approval was signed before taking blood samples. Levels of free carnitine and L-propionyl carnitine were analysed on Guthrie cards. Plasma samples were obtained for MDA analysis from cancer patients and control group.

Plasma samples were preserved at -80^0C until the time of analysis. Free carnitine and L-propionyl carnitine were studied on Tandem Mass Spectrometry with the method created by Millington et al[18] and MDA levels were measured with " high-performance liquid chromatographic" (HPLC) assay fluorometrically at Gazi University Pediatrics Metabolism Laboratory [19,20].

Statistic Analysis: Data were conducted with "Statistical Package for Social Sciences (SPSS 10.0)" program. The comparison between cancer patients and control group were estimated by using "Independent-Samples T Test" and comparison within patients with solid tumor were done by using Mann-Whitney U Test". The difference was accepted to be significant when statistical level (p value) was less than 0.05.

Results

The study was evaluated on 102 children consisting of 57 cancer patients with a mean age of 8.23 ± 4.37 years (27 female, 30 male) and a control group of 45 children with mean a age of 8.36 ± 4.41 years (28 male, 17 female). The distribution of a total number of 57 patients are as follows; 25 of them had lymphoma (7 had Hodgkin lymphoma and 18 of 25 had non-Hodgkin lymphoma), 8 of them had neuroblastoma, 8 of them had brain tumor, 6 of them had Wilms tumor, 10 of them had the other solid tumors (3 osteosarcoma, 3 Ewing sarcoma, 2 ovarian cancer, 1 fibrosarcoma, 1 thyroid tumor). When the weight of 57 patients were calculated; 1st degree malnutrition was found in 8 patients, 2nd degree malnutrition was found in 8 patients and 3rd degree of malnutrition was found in one patient according to Gomez criteria [21].

Free carnitine levels were found to be 33.60±15.40µmol/L in fifty seven patients with solid tumor and 30.80±8.63µmol/L in fourty five healthy children. A significant statistical difference was not found between the patients and healthy controls. While comparing the free carnitine levels in patients with solid tumor we found the highest value of 41.45±15.50µmol/L in the group of Wilms tumor and the lowest value of the carnitine was found to be 24.30±9.05µmol/L in neuroblastoma patients which was statistically significant ($p<0.05$). There were no significant differences between other types of tumors ($p>0.05$) (Table I).

Table I: Free carnitine levels of patients with solid tumor and control group.

Free carnitine (µmol/L) levels		
Diagnosis	**n**	**Average±SD**
Lymphoma	25	34.40±14.60 (9.57-62.30)
Neuroblastoma	8	24.30±9.05 (9.07-36.10)
Brain tumor	8	31.60±11.90 (16.60-57.80)
Wilms tumor	6	41.45±15.50(15.00-58.80)
Other solid tm	10	36.00±21.70(10.10-75.20)
Control	45	30.80±8.60 (12.80-48.30)

L-propionyl carnitine levels were found to be 1.07±0.55µmol/L in patients with solid tumor and 1.19±0.64µmol/L in healthy controls. There were no significant difference in L-propionyl carnitine levels between patients with solid tumor and healthy controls. When patients with solid tumor were analyzed according to the diagnosis, the highest L-propionyl carnitine value was found to be 1.53±0.35µmol/L in Wilms tumor patients, and the lowest value of L-propionyl carnitine was found to be 0.66±0.33µmol/L in patients with neuroblastoma. When the values of the patients with solid tumor were compared between each other, a statistical difference was found between Wilms and neuroblastoma patients ($p<0.05$). There were no significant differences between other tumors ($p>0.05$) (Table II).

Table II: L-propionyl carnitine levels of patients with solid tumor and control group.

L-propionil carnitine (µmol/L) levels		
Diagnosis	n	Average±SD
Lymphoma	25	1.12±0.64 (0.22-2.43)
Neuroblastoma	8	0.66±0.33 (0.11-1.13)
Brain tumor	8	1.10±0.50 (0.28-1.85)
Wilms tumor	6	1.53±0.35 (1.03-1.95)
Other solid tumor	10	0.98±0.37 (0.38-1.49)
Control	45	1.19±0.64 (0.18-3.54)

In patients with solid tumor, serum MDA level was found to be 2.47±0.64µmol/L as an average value. In control group, MDA levels were found to be 1.70±0.45µmol/L which was statistically significant compared to the patient group ($p<0.05$) (Table III).

Table III: MDA levels of the patients with solid tumor and control group.

*Malondialdehyde levels (*µmol/L)			
	n	**Average±SD**	**p**
Control	38	1.70±0.45 (0.92-2.93)	***<0.05***
Patients	57	2.47±0.64 (1.41-4.30)	

MDA level was also compared according to the type of solid tumor. The highest value was found to be 2.76±0.48 µmol/L in the group of brain tumor and the least value was found to be 2.09±0.32 µmol/L in patients with Wilms tumor. Which was statistically significant ($p<0.05$). There were no differences between other tumors ($p>0.05$) (Table IV).

Table IV. MDA levels of patients with the diagnosis of solid tumor

Malondialdehyde levels (µmol/L)		
Diagnosis	**n**	**Average±SD**
Lymphoma	25	2.37±0.68 (1.41-4.30)
Neuroblastoma	8	2.57±0.54 (1.99-3.26)
Brain tumor	8	2.76±0.48 (2.25-3.79)
Wilms tumor	6	2.09±0.32 (1.68-2.50)
Other solid tumors	10	2.66±0.77 (1.76-4.27)

When the nutritional status of the patients was analyzed, the free carnitine levels were found to be 34.44±16.13µmol/L in patients with solid tumor having malnutrition. The free carnitine levels were found to be 33.31±15.35µmol/L in solid tumor patients without malnutrition ($p>0.05$).

L-propionyl carnitine level of patients with solid tumor having malnutrition was found as 1.09±0.46µmol/L, while L-propionyl carnitine level of patients with solid tumor without malnutrition was found as 1.07±0.59µmol/L. There was no statistical significant difference between two groups according to the carnitine levels ($p>0.05$).

MDA levels were found to be 2.52±0.71µmol/L in 17 patients with solid tumor having malnutrition. MDA levels were found to be 2.45±0.61µmol/L in 40 patients with solid tumor without malnutrition. There were no significant difference between two groups ($p>0.05$).

Discussion

Carnitine is a micronutrient used by the body to transport long chain fatty acids to the mitochondria in cells where fatty acids are converted to adenosine triphosfate [3,22]. Researchers Sachan et al.[16] and Dodson et al.[23] found very low concentrations of serum carnitine and whole fraction of carnitine in cancer patients when compared to the control groups. Carnitine is absorbed in the body proximal to the tubular level through the kidney. Lack of carnitine may depend on a lot of factors. Insufficient production, increased necessity, excessive consumption and also loss of carnitine by kidneys may cause lack of carnitine levels. In the present research, we aimed to evaluate the carnitine levels of patients with newly diagnosed solid tumor according to control groups.

Yaris et al.[3] could not find any differences between the serum carnitine levels of patients with malnutrition in different degrees. Also when we compared the patients with solid tumor having malnutrition and the patients without malnutrition we could not find any significant difference between free carnitine, L-propionyl carnitine and MDA levels. As an antioxidant there was not a significant difference in L-propionyl carnitine levels in children with solid tumor and control group. We did not evaluate the effects of cardiac tumor, history of taking cardiotoxic medicine, antineoplastic usage such as anthracycline. In this study, the highest free carnitine and L-propionyl carnitine values were found in patients with Wilms tumor. Wilms tumor is the most frequently seen childhood tumors of kidney. Carnitine, lysine and methionine are mostly produced aminoacids in kidney [2]. The elevated levels of carnitine levels in Wilms tumor patients can be related with the increasing production of carnitine in kidney. Since our case number is limited and there is not a similar study in the literature, our findings should be supported by other studies including Wilms tumor patients. In this research; we also found the lowest levels of L-propionyl carnitine in neuroblastoma patients. Some neurotoxic products are produced as the way of anaerobic glicolysis by neuroblastoma cells [24]. This neurotoxic products may cause damage in electron transfering in fatty acid oxidation. The defect in electron transfering causes hipoglycemia, encephalopathy and secondary carnitine deficiency [24]. The carnitine decrease in neuroblastoma can be related with those neurotoxins. But this study must be supported with further researches including more patients with neuroblastoma. It is known that free O_2 radicals increase in patients with malignity. When these radicals and oxidant compounds like MDA attack membrane lipids, they damage membrane molecules' liquidity, permeability and structure by lipid peroxidation.

In our study, MDA levels of cancer patients were found higher than control groups ($p<0.05$). Serum MDA increase may depend on excessive tumor load and advanced stage of illness. Kergonou et al[25] revealed that radiotherapy increases lipid peroxidation.

In conclusion, MDA a serum lipid peroxidation product may be one of the important indicators of malignity. In practice, serum sample is more easily obtainable than tissues. Even if, serum levels of L-propionyl carnitine were found to be normal before treatment, its level may be changed in patients taking chemotherapy, radiotherapy and cardiotoxic medicine. Further research is needed including patients who require cardiotoxic chemotherapy. The patients in our study had many different types of malignancies. Unfortunately, the numbers of patients with each type of malignancy were too small to allow conclusions to be drawn with respect to potential differences in serum carnitine levels between the different malignacies.

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