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Investigation of Adenosine Deaminase, Aryl Esterase And Paraoxanaz-1 Serum Activities in Patients with Breast Cancer

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ABSTRACT

Aim: The purpose of the that study was to compare enzyme activities such as arylesterase (ARE), paraoxonase-1 (PON1), and adenosine deaminase (ADA) in patients with breast cancer. Materials and Methods: Adenosine deaminase (ADA), paraoxanase (PON-1) and arilesterase (ARE) activities were determined by spectrophotometer in the serums dissolved by centrifugation of blood samples from the patients with breast cancer. Results: The PON-1 activity of patient group (at phase-1, phase-2 and phase-3) was found significantly more lower than the healthy control group in breast cancerpatients ($p<0.001$). The serum ARE activity (at phase-1, phase-2 and phase -3) was found significantly morelower to control group in this thesis study ($p<0.001$). Then, in this study ADA activity was detected high in patient groups (at phase-1, phase -2 and phase -3) ($p<0.001$). Conclusion: In this study, the measurement of ARE, PON-I and ADA activities in breast cancer according to its stages in the literature is the first and a new study. As result, having a high level of PON-1 activity can be assessabled as a factor that reduces the risk of cancer that will be done.

***Keywords**: ADA, ARE, Breast Cancer, PON-1*

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INTRODUCTION

Breast cancer has been reportedin many literature studies that it is thethe most common cancer type in the world after lung cancer. It is the most common cancer type in females and constitutes 23% of all female cancers [1,2]. According to a study conducted in USA in 2011, one in eight females is at the risk of getting breast cancer for lifelong [3]. The important risk factors causing breast cancer are age, sex, race, cigarette, hormonal status, exposure to radiation, diet, lifestyle and socio-economic status.There are studies arguing that the risk of breast cancer increases in females who receive hormone theraphy compared to females who cannot receive hormone threapyin the postmenopausal period. The reason is shown as the increase in proliferation (proliferation of cells) with the exposure to hormone in the postmenopausal period. However, recent scientific studies don't show that the risk has increased [4]. Adenosine deaminase (ADA; EC 3.5.4.4, Adenosineaminohydrolase) catalyzes the formation of inosine and deoxyinosine by the seperation of ammonia from adenosine and deoxyadenosine in purine catabolism. ADA serum activity was high especially inlymphoid tissues. ADA is a key enzyme of purine metabolism. Serum ADA level is high in rheumatoid arthritis, tuberculosis and meningitis in various diseases caused by cellular immunity [5]. The decrease in ADA enzyme activity causes increase in intracellular adensine and deoxiadenosine. This situation may be toxic for molecular cell. Many factors have been identified as the cause of toxicity. As a result of their scientific studies, Sufrin et al. suggested that increased serum ADA enzyme levels were caused by primary tumor cells or lymphathic metastasis [6]. Free oxygen radicals (FOR) is the name identifying the single electron parts which aren't shared in atomic or molecullarstructures. These radicals are defined as free oxygen radicals (FOR) or reactive oxygen radicals (ROR) since they easily exchange electrons with other molecules [7]. Reactive oxygen redicals or free oxygen radicals are highly reactive atom and molecules due to their unshared electrons. Radiation, oxygen toxicity, postischemic reperfusion damage, infections and inflammations as well as aging-related diseases such ascataracts, atherosclerosis, carcinogenesis, diabetes and neurological diseases are among the reasons increasing the production of free oxygen radicals [8, 9]. The major intracellular antioxidants in human body are SOD, CAT, GPx, and PON-1 and ARE enzymes. And the extracellular antioxidant defense elements are vitamins Eand C, transferrin, haptoglobin, ceruloplasmin, albumin, billirubin, β – carotene ve α-l antitrypsin [10, 11, 12]. Paraoxanase (E.C.3.1.8.1); paraoxanase (PON-1) which is glycoprotein structure and a calcium-dependent ester hydrolase; is both arylesterase (ARE) (E.C. 3.1.1.2) and an enzyme withserum activity [13]. In humans and these are ranked as PON-1, PON-2 and PON-3. PON-1 enzyme, which is synthesized in human liver and released in blood, is a protein consisting of 354 aminoacides with weight of 43k Damolecules. PON-1 is more effective than vitamins A and E in terms of protection against oxidation due to its function [14,15]. PON-1 enzyme has an antioxidant function due to its capacity of neutralizing radicals.PON-1 enzyme activity was lower in organ transplant patients compared to the healthy individuals [16]. PON-1 serum level wasquiet low in the patients with Fish-eye and Tangier dieseases with lipid metabolism disorders due to HDL colesterol deficiency carrying serum PON-1 enzyme [17,18].In two different scientific studies by Akçay et al., it was observed that PON-1 level in the patients with pancreatic and gastric cancers had been lower than the control group. In another study; HDL and PON-1 levels were lower in cancer patients when the patients with gastric and pancreatic cancer and the healthy control group

were compared [19,20].Arilesterase (ARE) (E.C.3.1.1.2); Arilestrase (ARE) and paraoxanase (PON-1) are the enzymes in the esterase group whose active sites are similar and coded by the same gene. Although PON-1 shows polymorphic change, it is known that ARE enzyme doesn't show a genetic polymorphic change. Despite two enzymes having different natural substrates from each other, PON-1 enzyme has the capacity to hydrolyze phenyl acetate, the natural substrate of ARE. In the recent scientific studies, ARE has been updated due to its revealing antioxidant traits. It has been determined that ARE enzyme doesn't show any genetic polymorphic changes. PON-1 has an antioxidant function since it neutralizes radicals. On the other hand, ARE is considered as the main protein indicator which is not affected by the changes in PON-1[21]. In this study, it was aimed to measure some important enzyme activities according to stages in breast cancer patients.

MATERIAL AND METHOD

MATERIAL

The blood and serum samples in the study are from the patients who applied to Van YüzüncüYıl University Medical Faculty Oncology Clinic and were diagnosed with breast cancer.

METHOD

The study population consists of 25 patienst with breast cancer and 25 healthy individuals. The age range of the patients was between 35 and 60 years old. The age range of healthy individuals was between 32 and 62 years old. Biochemical parameters were identified with serum samples. Blood samples in the study were collected, the Approval of the Local Ethics Committee for Clinical and Laboratory Research in YüzüncüYıl University Medical Faculty Training and Before Research Hospitalhad been obtained. 3 ml of venous blood samples from healthy individuals and patients were centrifuged at 5000 rpm/dk for about 10 mins and thus the serums were dissolved. Adenosinedeaminase (ADA), paraoxanase (PON-1) and arilesterase (ARE) activities were determined by spectrophotometer in the serums dissolved by centrifugation of blood samples from the patients with breast cancer.

Analysis Methods

The Measurement of Adenosine Deaminase Enzyme Activity

Adenosine deaminase (ADA) enzyme activity was measured with First of all, 500 µL of Reagent 1 was put into spectrotub, 500 µL Reagent 2 was addedand mixed, then 250 µL of sample (patient serum) was added and the mixture was vortexed.The mixture was incubated in the oven for 4 minutes at 37C°. The mixture was firstly measured by spectrophotometer device at 340 nm. Then it was left to incubate again in the oven for 5 minutes at 37C°.As the second, it was similarly measured at 340 nm by spectrophotometer device. This process was applied for all samples. The results are expressed in Unit/Liter (U/L) which is equal to hydrolysis of one micmolar substrate per minute.The results were calculated according to the formula below.

Factor= [(50. 9 / 4^{th} minute Ast_1 – 5^{th}minute Ast_2)]

Result (U/L 37C°) = [(4^{th} minute As_1 – 5^{th}minute As_2) / 4^{th} minute Ast_1 – 5^{th} minute Ast_2)] x Factor [22].

The Analysis of Paraoxonase (PON-1) Enzyme Activity

Paraoxanase-1 activtiy was determined with a kit improved by Eren in 2004 and 2005. Paraoxanase-1 enzyme hydrolyzes paraoxon substrate in the reaction medium and the absorbance increase of the released product is monitored kinesteticall at a wavelength appropriate to the absorbance spectrum. The net values of enzymatic activity are calculated by substractingnonenzymatic hydrolysis value from the sample value. In this study, Rel Assay Paraoxonase kit was used and the measurements were determined with spectrophotometer device. Firstly, 500µL of Reagent 1 was put into a tube, then 25 µL of sample (patient's serum) was added and the mixture was vortexed. Next, 25 µL of Reagent 2 was added and the mixture was vortexed.Achronomometer was turned on at the exact moment of the adding. The absorbance value at 412 nm was quickly determined with spectrophotometer. The absorbance values were determined at the $30^{th}$and 150^{th} seconds. This process was applied for all the samples.The results are expressed at Unit/Liter (U/L) which is equal to hydrolysis of one micromolar substrate per minute.The results were calculated with the formula below.

Result (U/L) = [(150^{th} seconds AB_S – 30^{th} seconds AB_S) /2] x 1202. 84 [23].

Determination of Arylesterase (ARE) Enzyme Activity

The arylesteraseactivtiy was determined with a kit improved by Eren in 2004 and 2005. 990 µL of diluted solution was added onto 10 µLof serum. A dilution 10/1000 was carried out. The diluted solution 3 µL was taken and 260 µL of pure water (Reagent 1) was added, then 10 µL of Reagent 2 was addded onto it; afterwards, it was vortexed and measured at 548 nm.A_1 (first measurement) was identified. Then 80 µL of Reagent 3 was added to the solution in spectrotub. The solution was left at room temperature for 4 mins and measured as the second time, and identfied as A_2 (the second measurement). This process was applied for all samples. The aryl esterase enzyme activity was calculated according to the formula below

ARE (Enzyme Unit)=[(ΔA_2-ΔA_1)] x1316 [24].

Statistical Analysis

Arithmetic mean (X) and standard error (SEM) was statistically analysed by the computer program SPSS 15.0 for Windows' according to variance analysis of tukey's test. $p<0.05$ was considered significant.

RESULTS

When Table 1 was analysed in the measurement of ADA (adenosine aminase) enzyme activity, the statistical significant correlation was identified respectively as ($p<0.001$),

(p<0.001), (p<0.001) between the control group (24.89±1.58U/L) and Phase-1(37.41±1.21U/L), also Phase-2 (45.07±0.62U/L) and Phase-3 (58.34±1.27U/L).Also, the correlation between Phase.-1, Phase-2 and Phase-3 was identified respectively (p<0.001) and (p<0.001).When Table 4.1 was analysed for the determination of PON-1 (paraoxonase) enzyme activity, the correlations were identified respectively (p<0.001), (p<0.001), (p<0.001) between the control group(13.11 ± 0.42 U/L) and Phase-1 (4.46 ±1.14 U/L), Phase-2(0.51 ± 0.054 U/L) and Phase-3 (0.25 ± 0.056 U/L).Additionally, the correlations between Phase-1, Phase-2 and Phase-1, Phase-3 were identified respectively(p<0.001) ve (p<0.001).When Table 1 was analyzed for ARE (arilesterase) enzyme activity, the correlations were identified respectively (p<0.001), (p<0.001), (p<0.001) between the control grubu (236.40 ± 6.95 kU/L) and Phase-1 (47.49± 18.24 kU/L), Phase-2 (1.32 ±0.14 kU/L) ve Phase-3 (0.18 ± 0.024 kU/L). Also, it was identified respectively p<0.05 and p<0.05 between Phase-1, Phase-2 and Phase-1, Phase-3.

Table 1. ADA, PON-1 and ARE activities of the study population

Parameter	Control $\bar{X}$ ±SEM (n=25)	Phase-1 $\bar{X}$ ±SEM (n=8)	Phase-2 $\bar{X}$ ±SEM (n=9)	Phase-3 $\bar{X}$ ±SEM (n=8)
ADA (U/L)	24.89 ±	37.41 ± 1,21*	45.07 ±	58.34 ± 1.27*
PON1(U/L)	13.11 ±	4.46 ±1.14*	0.51 ±	0.25 ± 0.056*
ARE(kU/L)	236.40 ±	47.49± 18.24*#	1.32 ±0.14*#	0.18 ± 0.024*#

*: p<0.001 #:p<0.05

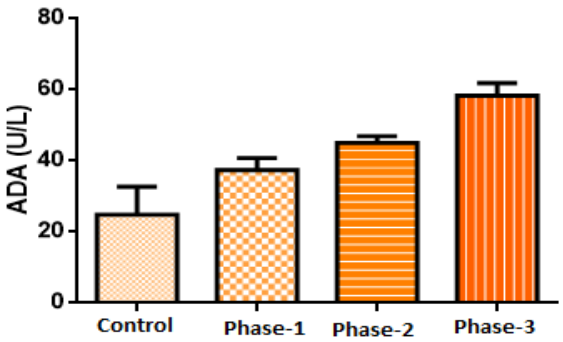

Figure1. ADA(adenosine deaminase) enzyme activity the comparision of the control and patient groups (Phase-1, Phase-2 and Phase-3).

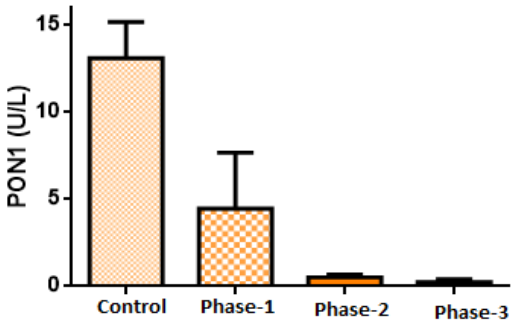

Figure2.PON-1 (paraoxonase) enzyme activity the comparision of the control and patient groups (Phase-1, Phase-2 and Phase-3).

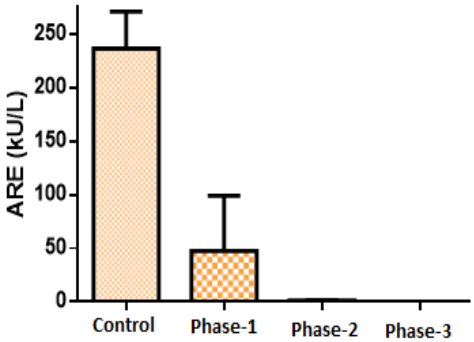

Figure3.ARE (arylesterase) enzyme activity the comparision of the control and patient groups (Phase-1, Phase-2 and Phase-3).

DISCUSSION and CONCLUSION

The enzymes eliminating free oxygen radicals has an important role in the protection of enzyme cells from oxidative stress.The correlation between well-known marker levels of oxidative stress measured as antioxidant status, lipid peroxides, oxidized proteins reflects a better health index and posture [25].In biological and biochemical systems, catalase (CAT), arylesterase (ARE), paraoxanase (PON-1), peroxidase (POD), glutathionereductase(GR) and superoxide dismutase (SOD) are the enzymes with antioxidant affects. The antioxidant defense system protects cell from oxidative damage by free radicals or other reactive molecules.Therefore, antioxidant enzymes such as CAT, PON-1, ARE, GR and SOD havegreat importance in this defense system.Breast cancer is a type of cancer occuring in breast cancer.In a study on breast cancer, serum PON-1 activity was measured on 110 patienst and serum PON-1 activities were identified to be less than the control group [26]. PON-1 activity was identified lowerin patients with lung and colorectal cancer, and even lower in those with breast cancer [26,27]. In this study, PON-1 activity in Phase-1, Phase-2 and Phase-3 was significantly lower than the healthy conrol group ($p<0.001$), (Table 1). And in the same study; while a statistical significance ($p<0.001$) was found between Phase-1, Phase-2 and Phase-3, there was no statistical significance between Phase-2 and Phase-3 (Table 1.). Also in studies, paraoxanase-1 enzyme may be a potential marker for survival in the patients with breast cancer recurrence [28].In literature studies,PON-1 activity decreased

in the breast cancerpatients.In same study, there were positive correlations between paraoxanase (PON-1) mutation and cancer risk[29].In a study, PON-1 levels were lower in gastric cancer patients compared to the healthy control group.In another study, it was stated that PON-1 levels were lower in pancreatic and gastric patients compared to the healthy control group [30,31]. PON-1 enzyme activity has been investigated in lung cancer patients and it was significantly low in lung cancer patients [32]. Our results support the literature data. As a result, high PON-1 activity level in blood can be considered as a factor reducing of cancer risk in future studies. In a study on breast cancer, serum ARE activities were low in the patient group [26]. In a research; ARE activity was lower in the patients with prostate cancer, lung cancer, neck cancer, Non-Hodking lymphoma and acute lymphoblastic lymphoma cancer than the healthy conrol group [33]. In a literature study on bladder cancer patients, serum arylesterase enzyme activities were significantly lower in the patienst group compared to the healthy control group ($p<0.05$). In the same study, low levels of arylesterase enzymes in the patients diagnosed with cancer is similar to many studies on relation of cancer [32,34]. In many literature studies, ARE enzyme activity was measured and determined to be relatively low similarly in the patients with lung cancer, endometrial cancer, epithelial ovarian cancer and esophageal cancer [32,35,36,37]. In a study by Akçay et al., ARE enzyme activity was examined in the patients with pancreatic and gastric cancer and determined that ARE serum activities were lower than the healthy control group [31]. In this study, serum ARE activity of Phase-1, Phase-2 and Phase-3 was significantly lower than the healthy control group ($p<0.001$) (Table 1). And while ARE activities in the patient group were statistically significant ($p<0.05$) respectively in Phase-1, Phase-2 and Phase-3, no statistical significance was identified between Phase-2 and Phase-3. Serum ARE level in types of cancer is generally low in studies. The data we have identified support literature results. Some studies has been searchedaboutthe relation between adensinedeaminase and various cancer diseases.In a study on cases with breast cancer by Aghaei et al., the activity of total ADA and ADA isoenzymes was evaluated in serum and tumor issue, and the relation between ADA activity and cancer progression was investigated. The activities of total ADA and ADA2 was higher in serum and tumor tissues compared to the control group. A strong correlation was determined between lymph node involvement, histological phase and tumor size of tumor ADA2 and total ADA activities; however, a positive correlation was determined between serum enzyme levels, menopausal status and patient's age [38]. In another study on 25 breast cancer cases by Walia et al.; ADA and 5'NT seum levels were significantly higher in cancer cases compared to the control group and a significant decrease was observed in the enzyme levels after mastectomy (removal of breast). As a result of the study, adenosine deaminase was suggested to be a valuable marker in the diagnosis of breast cancer and treatment follow-up. In a study by Saraçoğlu et al., ADA and 5'nükleotidaz activities were evaluated preoperatively and postoperatively in the saliva of 10 oral cavity cancers, 17 laryngeal cancer cases; and as a result of the study, ADA was lower in oral cavity cancer cases compared to the laryngeal cancer patients group and the control group. However, no statistically significant difference was observed in preoperative and post operative levels in terms of ADA and 5'NT in the patient group. Consequently, it was suggested that low ADA activity in the patients with oral cavity cancer might be a compensatuar mechanism against rapid purine and DNA metabolism, but it was concluded that these enzymes cannot be used as diagnostic and/or prognostic parameters [37]. While ADA enzyme activity increasedin many literature studies [9]. In the studies on laryngeal cancer cases by Canbolat et al. and on head-neck cancer cases by Lal et al., serum ADA

acivity was higher than the control group, but there was no significant diffeenceinpreopertive and postoperative levels.In the same studies, it was revealed that the enzyme activity levels decreased with radiotherapy [39,40]. In another study by Sufrin et al., serum adenosine deaminase (ADA) postoperatively decreased in lung cancer patients, also they suggested that increasing serum ADA levels were caused by primar tumor or metastasis[6].ADA and 5'NT decreased in the study on tumor tissues in laryngeal cancer patients by Durrak et al., and low lymphocyte ADA activity was identified in the patients with head and neck cancer in the study by Dasmahapatra et al. [41,42].In a study, mean values of total ADA and ADA2 activities of the breast cancer patients were significantly higher than the cancer group ($p<0.005$) and the healthy individuals ($p<0.0001$). In the same study, it was concluded that the evaluation of total ADA and ADA2 activities can be used as a reliable test to diagnose belign and malignant breast disease [43]. ADA activity was high in the cancer patients in another study on breast cancer patients [44].In a study on 20 patients with bladder cancer and 30 healthy individuals, serum adenosine deamiase was significantly higher in the bladder cancer patients compared to the control group($p<0.001$). These markers may be a potential finding as an additional biochemical diagnos tool for bladder cancer [45]. In this study, ADA activity levels of Phase-1, Phase-2 and Phase-3 were identified to be high in the patient group ($p<0.001$), (Table 1). And while there was no statistical significance for ADA activities respectively in Phase -1, Phase-2 and Phase-3 of the patient group, a statistical significance was determined between Phase-2 and Phase-3($p<0.001$) (Table1). Adenosine deaminase involving in purine metabolism has also increased in most types of cancer.Current findings are consistent with literature information [39,40,43, 44,45].In conclusion, oxidative stress and any damage to antioxidant balance can be considered as a possible reason of the breast cancer development. As result, having a high level of PON-1 activity can be assessabled as a factor that reduces the risk of cancer that will be done.Also, the measurement of ARE, PON-I and ADA activities in breast cancer according to its stages in the literature is the first and a new study.Webelieve that this study will contribute to future studies.

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