Oxidant/antioxidant status in serum of breast cancer women treated by surgical interference and chemotherapy

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ABSTRACT

Objectives: The study was designed to assess lipid peroxidation and oxidative defense system in patients with breast cancer, following them from the time of diagnosis through surgery and treatment. .

Patients and Methods: The study was conducted in Al-Jammhori Hospital, Mosul, Iraq. Twenty three women with breast cancer types III and IV and ٢٢ apparently healthy women as a control group were included in this study. Blood samples (٥ ml) were taken from patients and controls and analysed for serum malondialdehyde (MDA) and total antioxidant status (TAS) concentration. Blood samples were taken from patients one week before and after the operation and other blood samples were taken two weeks after the first dose of infusion with a combination therapy of cyclophosphamide, ٥-fluorouracil and doxorubicin. The therapy was started two weeks after the surgery every ٦ weeks for ٦ cycles.

Results: In breast cancer women, serum MDA was significantly higher ($P<٠.٠٠١$), whereas serum TAS was significantly lower ($P<٠.٠٠١$), compared with those of the control group. In patients, after breast surgery, serum MDA was decreased significantly ($P<٠.٠٠١$), while serum TAS was increased significantly ($P<٠.٠٠١$), compared with those of the patients before operation. Chemotherapy treatment caused a significant elevation ($P<٠.٠٠١$) in serum MDA associated with a significant reduction ($P<٠.٠٠١$) in serum TAS, compared with the patients before and after operation and also with the control group.

Conclusion: lipid peroxidation was increased in breast cancer women, while antioxidative defense system was decreased. Surgical removal of breast cancer decreased lipid peroxidation with an increase of antioxidant defense system. Lipid peroxidarion may be a consequence of cancer disease. Chemotherapy of breast cancer increased lipid peroxidation and depressed antioxidant defense system.

Keywords: breast cancer, lipid peroxidation, total antioxidant status, malondialdehyde.

الخلاصة

الهدف من الدراسة: صممت هذه الدراسة لتقييم زناخة الدهون ومنظومة مضادات الأكسدة في النساء المصابات بسرطان الثدي بدأ من التشخيص إلى الجراحة ثم العلاج.

طرق العمل: أجريت هذه الدراسة في المستشفى الجمهوري في مدينة الموصل/العراق. ثلاثة وعشرون امرأة مصابات بسرطان الثدي النوع 3 ومجموعة ضابطة مكونة من اثنين وعشرين من النساء الأصحاء. أخذت عينات الدم (5 ملم) من المريضات والمجوعة الضابطة وتم قياس تركيز مالونديهايد مصل الدم وتركيز مضادات الأكسدة الكلي في مصل الدم. أخذت عينات الدم قبل وبعد أسبوع من أداء الجراحة وأخرى بعد أسبوعين من أول جرعة علاجية. وكانت الجرعة العلاجية مكونة من سايكلوفوسفومايد (Cyclophosphamide) و 5-

فلورويوراسيل (٥-fluorouracil) و دكسوروباسين (Doxorubicin) وبدأت الجرع العلاجية بعد أسبوعين من إجراء الجراحة وكل ستة أسابيع ولمدة ستة دورات.
النتائج: كان تركيز مالنديهايد مصل الدم في المريضات المصابات بسرطان الثدي أعلى معنويا ($p < ٠.٠٠١$) فيما انخفض تركيز مضادات الأكسدة الكلي معنويا ($p < ٠.٠٠١$) مقارنة منه قي المجموعة الضابطة. وبعد إجراء الجراحة انخفض مالونديهايد مصل الدم معنويا ($p < ٠.٠٠١$) فيما لم تتغير مضادات الأكسدة الكلي معنويا مقارنة بالنتائج قبل العملية. كما أن العلاج السرطاني سبب ارتفاع معنوي ($p < ٠.٠٠١$) في مالونديهايد مصل الدم مصاحبا بانخفاض معنوي ($p < ٠.٠٠١$) في تركيز مضادات الأكسدة مقارنة مع المريضات قبل وبعد الجراحة وكذلك مقارنة مع المجموعة الضابطة.
الاستنتاج: ازدادت زناخة الدهون في المريضات المصابات بسرطان الثدي بينما انخفضت منظومة مضادات الأكسدة . إن ازالة سرطان الثدي جراحيا سبب انخفاضا في زناخة الدهون. ان زناخة الدهون قد تكون نتيجة مرض السرطان. وان العلاج المضاد للسرطان رفع من زناخة الدهون وقلل من منظومة مضادات الأكسدة الدفاعية.

Oxidative stress is implicated in the pathophysiology of breast cancer[١]. Generally, the increase of serum malondialdehyde (MDA) in breast cancer patients was supported by many workers[٢,٣]. However, plasma MDA was decreased in breast cancer patients[٤], The decrease in plasma MDA was associated with the severity of tumor size in breast cancer patients[٥].

Many studies found that plasma superoxide dismutase (SOD), catalase (CAT), total glutathione and vitamin A and E were decreased in breast cancer patients, suggesting the importance of endogenous antioxidants in the etiology of breast cancer[٦-٩]. On the other hand, glutathione peroxidase (GPX), and SOD were increased in breast cancer patients. Total antioxidant status (TAS) which is more valuable than individual antioxidants, was decreased in breast cancer patients[١٠].

Many studies showed that chemotherapeutic agents increases lipid peroxidation in cancer patients[١١,١٢], whereas total antioxidants were decreased by antineoplastic drugs[١٣].

The controversial results of lipid peroxidation in breast cancer patients and the interactions of individual antioxidants in the organism, noticed in the previous study, stimulated us to evaluate oxidative stress and antioxidant defense system in the cancer patients. The assessment was done by measurement of serum TAS instead of individual antioxidants. Other manipulation was used through measurement of serum MDA and TAS in the patients after removal of the cancer tissues. The study aims to examine lipid peroxidation and total antioxidant status in breast cancer patients following them from the time of diagnosis through surgery and treatment.

Patients and methods

This study received approval from Ninevah Directorate of Health (Medical Research ethical Committee). The study comprised ٢٣ women with breast cancer stage III from the breast cancer center at Al-Jammhori Hospital, Mosul, Iraq, during the period from February to November ٢٠٠٧. Their ages ranged between ٣٨ to ٦٠ years (mean±SD: ٤٩.٢±٥.٨ years). A control group of ٢٢ apparently healthy women were also included during that time from the same centre, their ages ranged between ٢٠-٦٨ years (mean±SD: ٤٩.٩±١٦.٦ years).

Blood samples (٥ ml) were taken from patients and controls, and analysed for serum MDA[١٤,١٥] and serum TAS[١٥,١٦] at the Department of Pharmacology, Mosul College of Medicine, University of Mosul, Iraq.

The blood samples were taken from the patients a week before and after the operation and other blood samples were taken two weeks after infusion of the first dose of chemotherapy. Combination drugs of cyclophosphamide ٥٠٠ mg/m^{٢}, ٥-fluorouracil ٥٠٠mg/m^{٢}, and doxorubicin ٥٠ mg/m^{٢} were started by infusion after two weeks of the surgery, every ٣ weeks for six cycles.

The exclusion criteria for both patient and control groups were any other disease, drug treatment, smoking or alcohol intake. Data are presented by mean ± SD. Paired t-test was used to compare between the follow up groups. Non paired t-test was used to compare between the control and patient groups.

Results

Serum MDA in the breast cancer women was significantly higher ($P < ٠.٠٠١$), whereas serum TAS was significantly lower ($P < ٠.٠٠١$) than that in the control healthy women (Table ١).

After surgery serum MDA deceased significantly ($P < ٠.٠٠١$), whereas serum TAS increased significantly ($P < ٠.٠٠١$), compared with the before operation in the patients (Table ١).

In post-operative patients, a combination of cyclophosphamide, ٥-fluorouracil, and doxorubicin elevated serum MDA significantly ($P<٠.٠٠١$) and reduced serum TAS significantly ($P < ٠.٠٠١$) compared with these values in post-operative patients before treatment (Table ١).

Table ١. Serum MDA and TAS in breast cancer and control women

	Serum MDA (µmol/L)	Serum TAS (mmol/L)
Control subjects N = ٢٢	٠.٩٨ ±٠.١٨	٢.٠٣ ±٠.٣٥
Patients N = ٢٣		
Before surgery	٢.٨٦ [a] ±٠.١٨	١.٣ [a] ±٠.١١
After surgery	٢.٧١ [b] ±٠.٢	١.٣٥ [b] ±٠.١٢
After chemotherapy	٣.٠٤ [c, d] ±٠.١٦	١.٠٧ [c, d] ±٠.١٤

[a] $p<٠.٠٠١$ VS. Control, [b] $p<٠.٠٠١$ VS. before surgery; [c] $p<٠.٠٠١$ VS. after surgery, [d] $p<٠.٠٠١$ VS controls.

Discussion

This study attempted to clarify the controversial results in the literatures for lipid peroxidation and antioxidant defense system in breast cancer patients. Serum MDA and TAS were measured before and after removal of breast cancer in the studied patients. In addition, serum TAS was measured instead of individual antioxidants, since it covers all enzymatic and non-enzymatic antioxidants[١٦].

In the present breast cancer women, serum MDA was increased with a significant reduction of total antioxidant defense system compared with the control group. These results are consistent with other studies[١٧,١٨]. However, lipid peroxidation and individual antioxidants in the blood of breast cancer patients are still controversial[٥,١٩-٢٢].

The change in lipid peroxidation in breast cancer as a cause or consequence remains to be clarified. Torun et al.[٢٣] suggested that measurement of MDA levels provides useful information in evaluating breast cancer. In the present breast cancer patients, surgical removal of breast cancer depressed serum MDA suggesting the implication of the breast cancer in causing lipid peroxidation.

After one week of surgical removal of the present breast cancer, serum TAS was significantly increased. The time of one week after surgery may be enough to regenerate the antioxidant defense system possibly reflecting the relief of oxidative stress caused by removal of the cancer. Erohla et al.[٢٤] surgical removal of lung cancer caused a reduction in total antioxidant capacity during the early hours after operation but after few months of surgical removal of the tumor, there was an augmentation in total plasma antioxidant.

In the present study, chemotherapy for the breast cancer showed a significant increase in serum MDA. These results are consistent with other workers[٢٥]. Serum MDA in the treated patients was even higher than that in the patients before surgery. There is evidence that anticancer drugs exert their cytotoxic activity by free radical mediated mechanism[٢٦]. In addition, suppression of cancer growth was enhanced by pro-oxidants[٢٧].

Mitochondria are the main site for reactive oxygen species (ROS) generation and are thought to be a major intracellular target for oxidative damage[٢٨]. Anticancer agents can cause mitochondrial permeabilization through enhanced generation of lipid peroxidation, and once the mitochondrial membrane barrier function is lost, several factors contribute to cell death[٢٩]. Moreover, Mitochondrial permibilization was facilitated by lipid peroxidation and antioxidant enzyme inhibited it[٣٠]. Tandon et al. [٣١] suggested that oxidative stress is not always detrimental, as it can be beneficial in cancer sometimes. Hence, oxidative stress can be as a double way sword in malignant states[٣١].

Serum TAS was significantly decreased by chemotherapy compared with that before treatment, the free radical mediated mechanism of chemotherapy may exhaust the antioxidant defense system.[٢٩]. In addition, the dietary depletion of vitamin E and vitamin A inhibited mammary tumor in mice[٣٢].

In conclusion, breast cancer increased lipid peroxidation and depressed antioxidant defense system. Removal of breast cancer in women decreased lipid peroxidation. Lipid peroxidarion may be a consequence of cancer disease. Chemotherapy of breast cancer increased lipid

peroxidation and depressed antioxidant defense system in breast cancer women.

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