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Superoxide Dismutase Activities in Plasma of Patients with Breast Cancer

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ABSTRACT

Background: Superoxide radicals are produced during oxidative metabolic processes, and removed by superoxide dismutase (SOD) enzymes. Controversial results have been reported regarding the tissue and plasma concentration of SOD in patients with breast cancer.

Methods: From study participants including 100 women, venous blood samples were obtained and activity of SOD enzyme was determined. The comparison was between 50 patients with breast cancer and 50 individuals in control group.

Results: The activities of SOD in patients with malignancy and control group were 553.56±53.67 U/gr Hb and 1218.60±98.55 U/gr Hb, respectively ($p<0.001$). Patients with higher stage and nuclear grade had lower SOD activity.

Conclusions: Lower levels of SOD activity was observed in women with breast cancer compared to healthy individuals. Considering the existing controversy regarding the SOD level in breast cancer patients, further studies are suggested to explore the reason of these differences.

Introduction

Superoxide radicals are produced by a wide variety of human cells during oxidative metabolic processes. They are potentially toxic and based on their concentrations can lead to cellular injury or even to cellular death.[1,2] Mutations due to DNA damages caused by high concentration of free radicals, play pivotal role in cancer pathogenesis.[3,4] Carcinogenetic role of free radicals is supported by high levels of free radicals in cancer cells.[5]

Superoxide radicals are removed by superoxide dismutase (SOD) enzymes and are converted to molecular oxygen and hydrogen peroxide. It has been reported that not only free radicals concentration is increased in malignant cells, but also the levels of SOD are diminished.[5] Research is ongoing on the role of free radicals in pathogenesis of breast cancer and controversial results have been reported regarding the tissue and plasma concentration of SOD in patients with

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breast cancer.[6-11]

It is also speculated that oxidative stress and the defense status of cancer cells against it, may be related to the outcome of patients and could be of prognostic value. In this regard, it has been reported that antioxidant protein expression predicts response to radiotherapy and is associated with the rate of recurrence.[12]

In this study we investigated differences between plasma activiti of SOD in breast cancer patients versus control group. Additionally, the association of several tumor features and SOD activity was investigated.

Methods

A case-control study was initiated to compare the activity of SOD among patients with breast cancer and control group in a referral teaching hospital in Tehran, Iran between May 2010 and November 2012. Study protocol was in accordance to latest Helsinki Declaration for investigation on human subjects. Local ethics committee at Tehran University of Medical Sciences approved the study protocol.

Case group comprised of 50 women admitted at surgery ward. The final diagnosis of breast cancer was established for them through histopatholo-gical examination of breast tissue obtained by either core needle or open biopsy.

Control group was selected from patients attended to outpatient breast surgery clinic of the same hospital, in whom malignancy was ruled out through careful and appropriate clinical and paraclinical assessments.

Patients' demographic and clinical information were recorded. A total of 5cc of venous blood was obtained in heparinized tubes and centrifuged at 3000 g for 10 minutes. Packed cells were transferred to laboratory to determine total SOD activity using RANSOD kit (Randox lab., Crumlin, Northern Ireland).

Statistical analysis

Statistical analyses were performed using SPSS, version 20 (IBM Inc., NY, USA). Continuous variables are presented as mean and standard error of mean (SEM), while categorical parameters are shown as percentage. Plasma level of SOD was compared between study groups using independent t-test.

Results

A total of 100 patients were recruited with mean age of 39.55±10.46 years. Patients in case group had mean age of 47.88±5.75, while those in control group were 31.22±6.82 years old (P< 0.001). Such differences were not observed comparing body mass index (BMI) between the two groups(cases: 26.64±2.52, controls: 26.74±2.64).

The activities of SOD in patients with malignancy and control group were 553.56±53.67 U/gr Hb and 1218.60±98.55 U/gr Hb, respectively. This difference was statistically significant (P< 0.001). Considering clinicopathological characteristics of subjects with breast cancer, patients with nuclear grade 3 had lower SOD activity than patients with nuclear grade 1 and 2 (369 vs 756 U/mg Hg) (P< 0.001). Patients with stage 3 cancer also had lower SOD compared to patients in other stages (527 vs 1003 U/mg Hg) (P< 0.001). There were no associations between blood group, patient age, estrogen intake and SOD activity.

Discussion

We found that SOD activity is lower in patients with breast malignancy in comparison with the control group. This was consistent with other studies reporting similar results.[6,7] These findings have shown that antioxidant defense systems are significantly impaired in patients with malignant breast tumor. Diminished SOD enzymes level renders cells to accumulate free radicals. An imbalance between production of free radical oxidase and defense mechanisms that scavenge them has long been thought to be an important factor contributing to pathogenesis of cancer.[13] In addition, we found that there is a statistically significant association between SOD and tumor stage and grade. In this regard, patients with nuclear grade 3 had lower SOD compared to other patients. This is in agreement with Sinha *et al* findings that reported plasma SOD level is higher in patients with early stage breast cancer compared to advanced ones.[7]

In contrast, a higher level of SOD in breast cancer patients has been documented in some other studies. It has been suggested that once malignant transformation occurs, cancer cells develop protective mechanisms to suppress further proliferation through antioxidant systems.[14] Meanwhile, others postulated that elevated total SOD might reflect a response to oxidative stress, and thus may predict a state of excess reactive oxygen species in the carcinogenesis process.[15]

Researchers have suggested that while oxidative stress and inadequacy of antioxidant mechanisms can lead to malignancy, after transforming to cancer, SOD may have a role in disease promotion. Kamarajugadda *et al* have reported that MnSOD level is elevated in breast cancer metastases that promote resistance to anoikis, an apoptosis that follows detachment of cells from extracellular matrix, thus MnSOD can contribute to metastasis.[16]

Role of antioxidant defense mechanisms in carcinogenesis have brought them into attention as

diagnostic and therapeutic targets.[17] Manello *et al* have shown that SOD level in nipple discharge was lower in patients with breast cancer in comparison to control group.[18] Further studies are needed to approve such findings and make them clinically applicable. Therapeutic strategies have been proposed based on contradictory role of ROS in cancer cells. Although low levels of ROS can induce pathways that promote cell proliferation,[19] overwhelming ROS content higher than required level for proliferative signaling may cause oxidative damages that lead to cellular death and apoptosis.[20] Therefore, one therapeutic approach would be to increase ROS scavengers such as SOD that inhibit cell proliferation, while the other one would be to suppress antioxidant mechanisms resulting in high levels of ROS and triggering cell death.[21]

This study suffered from some limitations like the selection of control group from women attended to our breast clinic, and relatively small number of enrolled patients.

In conclusion, lower levels of SOD activity was observed in women with breast cancer compared to healthy individuals. Considering the existing controversy regarding the SOD level in breast cancer patients, further studies are suggested to better understand the reason of observed differences.

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