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Superoxide Dismutase and Its Cofactors, for Serum and Salivary Levels in Breast Cancer Patients

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Abstract

Background: Breast sarcoma is the most regularly diagnosed malignancy among females. Another source of specimen for clinical diagnosis is saliva which has been utilized and it is a hopeful approach as collecting saliva is relatively easy and non-invasive. Over the past two decades, developing saliva as a bio-pointer, precisely for early malignancy identification has appealed much research attention.

Aim: To examine and compare blood and saliva samples in order to measure antioxidant components such as Superoxide Dismutase (SOD) and trace elements in order to detect a simple, early, and noninvasive diagnostic test as biomarkers and prognostic tools in breast cancer patients.

Methods: A total of 96 female volunteers were participated in this study, 50 patients with breast malignance compared with 46 healthy participants in order to evaluate and compare salivary and blood level enzyme such as SOD with some trace elements such as: Copper (Cu), Manganese (Mn), and Zinc (Zn).

Results: The mean serum and salivary samples data presented that the levels of SOD ($P<0.001$), Cu ($P<0.01$), Mn ($P<0.001$), and Zn ($P<0.05$, $P<0.01$) were significantly reduced in breast melanoma illnesses than those of non-breast melanoma illnesses.

Conclusion: In this study, salivary levels of SOD and some trace elements were compared to blood levels to see if they could be used as a non-invasive diagnostic tool instead of serum testing component, which might be used as biomarkers and tumor progression evaluations in diagnosing breast sarcoma.

Keywords: Breast cancer; Copper; Manganese; Superoxide dismutase; Zinc

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Introduction

The electron reduction from oxygen can generate Reactive Oxygen Species (ROS) forms such as hydroxyl radical, superoxide anion, hydrogen peroxide, etc. [1,2]. ROS act critical parts in pathogenesis of chronic diseases on top of cancer and similarly in the mechanisms of numerous therapeutic modalities e.g., chemotherapy and radiotherapy [3]. Breast malignancy is the most recurrently noticed and shattering melanoma category that caused of death among women universal [4] and also in Iraq too [5]. It is treatable, if it is early identified [6]. ROS in biological organisms is preserved in a vibrant balance by a chain of reduction-oxidation (redox) reactions and act as signaling molecules to initiative cellular regulatory metabolisms [7]. Supreme oxidative tension ensuing from ROS buildup releases the anti-oxidative resistance arrangement that meticulously allied with numerous diseases and carcinomas [8,9]. Though, the cell shield from harmful activities of free oxygen reactive (e.g., ROS) kinds, which is executed by Superoxide Dismutase (SOD) [10]. SODs are widespread enzymes of human that act in the existence of oxygen. They produced oxygen and hydrogen peroxide from superoxide. It was consequently well-known that SODs are the first track for guarding against active oxygen free radicals. The SODs have been classified three types existing in countless organisms owning diverse cofactors such as: Cu/Zn SOD1, Mn SOD2, and extracellular Cu/Zn SOD3 [11]. SOD is an enzyme comprehended to safeguard DNA, molecules of cell membrane and proteins produced from oxidative distractions. The vital characters of trace elements are by regularizing the immune system, mitochondrial and enzyme activity nerve contraction, mitochondrial activity. The revisions have been testified the association of too plenty metal concentrations with diseases, e.g., breast malignancy gastrointestinal sarcoma, leukemia, lung malignancy [12-14]. Till this moment the trace elements mechanism for causing sarcoma in biological

system is anonymous. Nevertheless, revisions on the connotation between the reasons of sarcoma and the elements concentrations are in great importance [15]. Total saliva is located in the oral cavity (mouth), which is a combination of water excretion made by chief salivary glands, minor salivary glands, and gingival crevicular liquefied excretions with consisting of potentials of biological fluid with amazing prospects for the investigation [16], and can be utilized as detecting for illnesses [17]. In general diseases, lead to salivary gland dysfunction. Minerals in the salivary have adequate vital parts such as inducing of plenty enzymes activities, urbanized bone and teeth, stopping tooth decline, neutralizing oral cavity environment, and etc. [18]. Hence the current investigation is directed at presuming specific of the biomarkers, straight connected with breast malignancy, which are low-cost, precise, known by easy ways for detection and certified, that may perhaps be of some analytical significance [10]. Even with the wide investigation for lots of years, the etiopathogenesis of sarcoma still leftovers uncertain. Numbers of biochemical indicators have been deliberate to assess the carcinoma for the early recognition in numerous origins [19]. The object of this research paper is to alter the sample collection from blood to saliva for some components such as SOD with some trace elements, in order to detect an easy, earlier and noninvasive diagnostic test as biomarkers and prognostic tools in patients with breast sarcoma.

Materials and Methods

A whole of 96 female volunteers were participated in this research, 50 patients that newly diagnosed and untreated with breast malignance (4^{th} stage) compared with 46 healthy volunteers in the age range of 40 to 69 years. The samples (saliva and blood) have been randomly collected from fasting patients attended Nanakali Hospital in Erbil city, Iraq. Under resting conditions, 8 ml of unstimulated salivary samples were taken by spitting method between 10:00 am to 11:00 am, at the same time 7 ml of the blood samples were taken too from each participant. The samples centrifuged and stored in disposal tubes without anticoagulants and have been well-kept in ice-box then the samples have been moved to laboratory in order to evaluate and compare both salivary and blood level of enzyme such as SOD with some trace elements such as, Cu, Mn, and Zn concentrations in breast malignancy and healthy subjects. The trace elements parameters: Cu, Mn, and Zn concentrations were tested by using instrument known atomic absorption spectrometer ST-AAS 7000 Series. While BioVision kit was utilized to detect the SOD activity that measured by instrument called ELISA. The SPSS 22.0 software package was utilized to evaluate the data. The results are expressed as mean ± SD our date was analyzed statistically utilizing paired t-test to compare subjects result for a number of parameters among altered groups tested in this work.

Results

The mean serum samples data presented in Figure 1, showed that the levels of serum SOD ($P<0.001$), Cu ($P<0.01$), Mn ($P<0.001$), and Zn ($P<0.05$) were significantly dropped in breast sarcoma patients when compared with control subjects. Figure 2 displayed that the salivary concentrations of SOD ($P<0.001$), Cu ($P<0.01$), Mn ($P<0.001$), and Zn ($P<0.01$) were significantly reduced in breast malignancy when compared with healthy participants likewise in serum levels.

Discussion

Breast malignancy is categorized by elevated oxidative stress, an inequality among ROS and antioxidants. Enriched ROS accumulation, as outcome of pathway disorders and signaling irregularities, can induce sarcoma [20]. The ROS amounts are confidently controlled by antioxidant schemes, which involving non-enzymatic antioxidant and enzymatic antioxidant pathways. The changing of enzymatic activity in body is characterized as biomarker [21]. Numerous enzymes and its iso-enzymes are a lot utilized as signs in identification of sarcoma sicknesses. Even though these enzymes symbolize results of carcinoma cells, they are still not too precise for malignancy for the reason that they can from time to time alter in some additional illnesses [22]. The cells adjust metabolic in order to hold (normalize) oxidative stress, thereby improving making of SODs, NADPH, glutathione, and thioredoxins to return ROS to normal concentrations [23-25]. Plentiful antioxidants were established, and classified as enzymatic antioxidants, e.g., SOD [26,27], with nonenzymatic antioxidants, e.g., vitamins and trace elements [28]. The metalloprotein SODs are antioxidants that professionally utilized to remove free radical from oxygen by a dismutation pathway [29]. There are two types of free radicals; first endogenous free radicals that are formed during oxidative pathway, the other one is exogenous free radicals that created by revelation to motivations e.g., UV light or certain chemicals, which eradicated by SOD [30]. Figure 1, 2 are detected significant reduced levels of SODs activities in both blood ($P<0.001$) and saliva ($P<0.001$) samples of breast cancer as compared with healthy subjects in this research paper. So, SOD was urbanized as a medication in order to preserve against oxidative stress [29]. Likewise, our data Negahdar et al. [31] revealed that the activities of SOD and catalase reduced just in the whole blood of breast melanoma. Besides Yuksel et al. [32] detected that the activities of SOD, nitric oxide, glutathione, and hydrogen peroxide were decreased when treated with sodium butyrate in breast cancer cells. In contrast Xi et al. [33] spotted that the SOD activities improved. Additionally, the activity of SOD1 (CuZnSOD) is strictly linked with Cu and Zn amounts [34].

The pathogenesis of certain breast malignancies have been allied with variations in the balance of numerous trace elements [35,36], for example Zn. There is a homeostatic arrangement of Zn between Thionein (T) and Metallothionein (MT). At what time the diet of Zn in the body is enough, Zn is stored as a form of MT by binding with T. When the quantity of element Zn is truncated, Zn is free from MT [37]. So, the connection between Zn and breast malignancy may be similar to a double edge sword; additional or shortage of Zn may have opposing influences [13]. Furthermore, once the body has slight amount of Zn, the CuZnSOD creation is reduced and ROS is amplified. So, Zn preserves the production of the CuZnSOD active, which can successfully defeat cancer cell evolution [38]. Thus, the outcome results of current paper displayed that the mean ± SD levels of serum and saliva Zn in patients with breast melanomas were significantly lower than those of non-breast melanomas participants in mutually serum ($P<0.05$) and saliva ($P<0.01$) samples significantly and this was agreed with the above clarifications. Moreover, Khalid et al. [39] in Asia and Joy et al. [40] in Africa support our study by revealing the reduced amount of Zn level significantly in the plasma/serum of illnesses with breast malignancy. Likewise in a meta-analysis Feng et al. [41] explained that the serum Zn amounts were statistically diminished, but contrariwise connected with Cu levels, which are higher in breast carcinoma sicknesses. Cu is individual of the vital trace elements for the wide-ranging population. Enterocytes obtaining Cu for their specific regular cellular functions, e.g., respiration of the mitochondrial [42], linked closely with SOD1 [34] and ROS detoxification [42]. So, decline of Cu leads to improve of

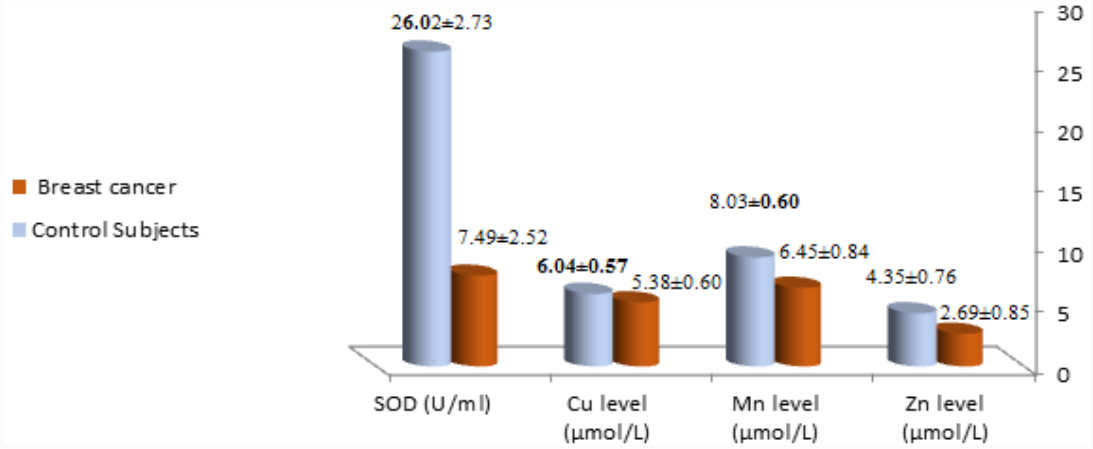

Figure 1: Superoxide Dismutase (SOD) with some trace elements such as: Cu, Mn, and Zn levels in blood samples of healthy controls compared with breast cancer patients (Values are expressed in mean ± SD).

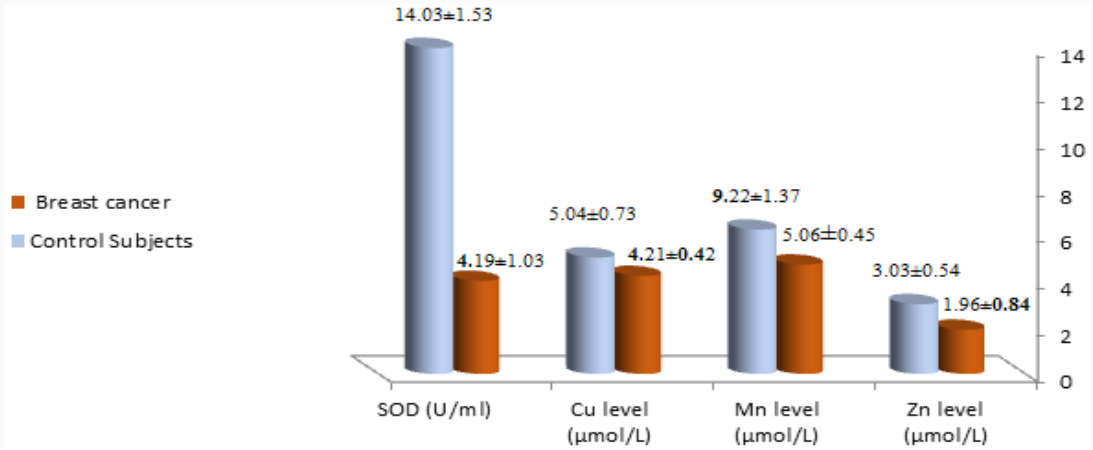

Figure 2: Superoxide Dismutase (SOD) with some trace elements such as: Cu, Mn, and Zn levels in salivary samples of healthy controls compared with breast cancer patients (Values are expressed in mean ± SD).

ROS and induced carcinoma due to the reducing of CuZnSOD complex [20,43], and this can be seen in existing study that low levels of Cu amount significantly are related to breast carcinoma cases in both samples' serum (P<0.01) and saliva (P<0.01) (Figure 1, 2). Cui et al. [44] were discovered significant diminish of mitochondrial Cu in breast carcinoma of mice and connected with carcinoma evolution, which swings pathway from respiration to glycolysis and diminishes energy making, is recognized to be in effect against malignancy categories. Still, present Cu chelators are very toxic or useless for carcinoma treatment. In a case report proved that serum level of Cu was depleted in breast carcinoma with Wilson disease [45].

Another important and universal population trace element is Mn, which is effortlessly oxidized [46]. Mn cations are the operative precinct of MnSOD enzyme that is responsible of the ROS detoxification [47]. This may be the reason that the concentration of Mn decreased in each serum (P<0.001) and saliva (P<0.001) significant statistically breast melanomas disease than those of non-breast melanomas disease these were displayed in Figure 1, 2 which a meta-analysis research in plasma and serum of Mn level in illnesses with breast malignancy was statistically lesser than the healthy participants [48] and extra study established that Mn concentration was significantly reduced in carcinomas breast sickness support this current data [35]. Identical to CuZnSOD, when the blood Mn level is little, means there is not sufficient Mn to uphold the structure of the site activity of MnSOD, thus indorsing quick malignancy cell evolution [49]. Saliva has salivary indicators that are utilized in the identification of sarcoma, cardiovascular sicknesses, etc. [50]. Identification of diseases by saliva is an evolving area with gratitude as it covers hormonal rank, neurological influences, nutritional and pathway effect and immunological rank, the identification biomarkers are too beneficial in numerous analyses [51]. Limited study done on saliva as a bio-pointer so it needs more research in this field.

Conclusion

In this study the changing of salivary levels of SOD and some trace elements as compared with blood may be used as a non-invasive diagnostic tool alternative to serum testing components, which were significantly declined in patients with breast malignancy in blood and saliva and also, may be utilized as biomarkers and tumor progression assessments in identifying of breast sarcoma.

In this instigation the subsequent conclusion can be pinched from the study that the levels of blood and saliva samples of some antioxidant e.g., enzymatic antioxidant (SOD activates), and non-enzymatic antioxidant (Cu, Mn, and Zn) were lowering significantly

in breast cancer. The changing of salivary levels of SOD and some trace elements as compared with blood may be used as a non-invasive diagnostic tool alternative to serum testing components, which were significantly declined in patients with breast malignancy in blood and saliva and also, may be utilized as biomarkers and tumor progression assessments in identifying of breast sarcoma. Alongside saliva may well signify as an active new gate as blood assessment but easier and chipper.

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