Revision of some Biomarkers with Cytokines in Breast Cancer

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Abstract:

Breast cancer is the most repeatedly detected cancer category and the second reason cause of cancer-linked deaths among women worldwide. Tumor bio-indictor is a term utilized to describe possible indicators for carcinoma diagnosis, development and progression. The goal of this study is to evaluate part of some cytokines and biomarkers for both serum and saliva samples in breast cancer then estimate their potential value in the early diagnosis of breast cancer by doing more researches in saliva, and utilizing saliva instead of blood (serum and plasma) in sample collection from patients. Serum and salivary samples were taken from 72 patients with breast cancer and 45 healthy controls, in order to investigate the following cytokines such as: interleukin 12 (IL-12), interleukin 6 (IL-6), interleukin 4 (IL-4), 8-hydroxydeoxyguanosine (8-OHdG), tumor necrosis factor (TNF) and interferon-γ (IFN-γ) levels with other bio-pointers such as: malondialdehyde (MDA), catalase, and 8-nitroguanine (8-NG). The results displayed that the levels of blood and saliva samples of IL-12 ($P<0.0001$), IL-6 ($P<0.0001$), IL-4 ($P<0.001$), 8-OHdG ($P<0.0001$), 8-NG ($P<0.001$, and $P<0.004$), TNF ($P<0.002$, and $P<0.001$) and IFN-γ ($P<0.0001$) were significantly higher in breast cancer, whereas there were significant lowering ($P<0.0001$) in catalase activates in breast cancer in both samples as compared with healthy subjects. The exchanging of blood to salivary components evaluation in this investigation may be utilized as a diagnostic tool, and designates the potential part for MDA, Catalase, and cytokines as important biochemical in breast cancer. Accordingly, the salivary diagnosis embraces a non-invasive process and tumor progression in breast malignancy patients. Beside saliva may well signify as an active new gate as blood evaluation but easier and cheaper.

Keywords: Breast cancer, Catalase, Cytokines, Malondialdehyde, 8-Nitroguanine.

Introduction:

Breast cancer is the most repeatedly detected cancer category and the second reason cause of cancer-linked deaths among women worldwide[1]. The origins of breast cancer are not yet completely acknowledged, even though a number of threat elements have been known [2]. The dying-to-living proportion in breast cancer has been declining over the years, which designates that the survival rate is progressively elevating [3]. Even with the notable improvements in scientific facts, the hazard factors and the mechanisms in charge for breast cancer are under analysis yet [4]. Biochemical is relating to the chemical processes and substances which occur within living organisms and can be used to designate potential indicators of cancer diagnosis, development and progression [3]. Cytokines are extremely inducible, secretory proteins that facilitate intercellular communication in the immune system. They are grouped into numerous protein classes such as tumor necrosis factors, interferon's, interleukins, and colony-stimulating influences [5-6]. IL-4 deeds as antitumor and anti-inflammatory effects, even though play on B lymphocytes, dendritic cells, monocytes, fibroblasts, and assessing allergic responses [7]. IL-6 is formed by vascular endothelial cells and mononuclear phagocytes fibroblasts. TNF and Interleukin 1 (IL-1) stimulated IL-6 excretion which acts chiefly on hepatocytes and B cells. Interleukin-6, acting as the chief stimulator of the inflammatory reply, conducts the prime character in the pathology and angiogenesis of cancer [8]. One of the finest-categorized phenotypes in malignancies is high amount of reactive oxygen species (ROS) [9-11], which has been distinguished in nearly whole cancers. The grade of oxidative stress can be better

assessed by examining oxidative responses because of its great instability. 8-hydroxy-2-deoxyguanosine (8-OHdG), a formed from of oxidative destruction to 2-deoxyguanosine and 8-nitroguanine (8-NG), which is identified as a beneficial indicator for determine oxidative DNA break down and has been a feature of malignancy in several seeks [12-14]. The IFN-γ is perforin and granzyme excreted by cytotoxic natural killer and T cells, these can encourage the programmed cell death (apoptosis) of malignancy and regulated tumor growth. Besides, IL-12 aids antigen appearance by controlling major histocompatibility complex class I on swelling cells, which can encourage the evolution and function of T cells [15]. Catalase is a momentous antioxidant enzyme that transformes H_2O_2 into H_2O and O_2. The catalase gene has the features of a guarding gene and it is a core organizer that is vastly sealed among classes that effectually extract ROS [16]. MDA is the substance (end product) formed from breakdown of lipid peroxidation [17]. The oral cavity contains salivary glands that excreted a clear liquid which some extent acidic called saliva. Numerous years of exploration with research in order to document the range of substances in saliva, and this has unlocked a new gate of salivary diagnostics as new venues. Also it is noninvasive, which prompt collection method. Saliva consists of the qualities of biological fluid with extraordinary probabilities for the analysis, and can be utilized as monitoring of sicknesses [18]. The object of this article is to utilize cytokines and bio-indicators for diagnosis of breast cancer cases, and utilizing of saliva instead of blood (serum and plasma) in sample collection from patients, which is easier and cheaper.

Materials and Methods:

One hundred seventeen participants were recruited and enrolled in this trial embraced 72 cases of diagnosed females with breast cancer (newly diagnosed/ untreated/4th stage) and 45 healthy controls at ages ranging from 29-64 years. The samples have been randomly collected form female attended Nanakali Hospital for groups, in Erbil city, Iraq. The blood samples have been claimed after overnight fasting. The serum has been prepared by collecting 7 mL of the blood with and without anticoagulant, and then serum and plasma have been separated by centrifugation. Un-stimulated saliva has been claimed from the same patient after diagnosis, under resting conditions between 8:00-9:00 AM. Saliva has been collected by spitting method into a wide test tube (10 mL) and then it has been centrifuged. The biochemical assessments have been carried out instantly. Every blood sample and saliva has been examined
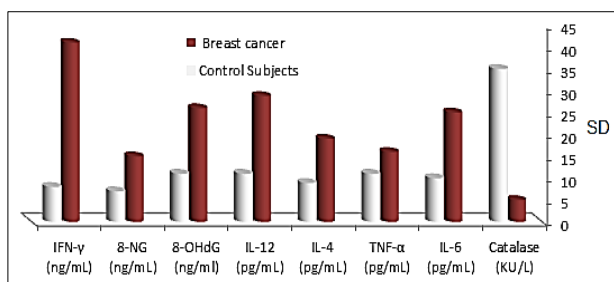
according to the following parameters: MDA, catalase, IL-6, IL-4, 8-OHdG, 8-NG, TNF and IFN-γ amounts. The measurements of MDA, and catalase have been valued by utilizing the Randox kit conferring to the procedure explained by the manufacturer utilizing spectrophotometric instruments (BioTek Instruments, Milan, Italy), while IL-6, IL-4, 8-OHdG, 8-NG, TNF-α and IFN-γ concentrations have been valued by utilizing the ELISA (sandwich enzyme linked immunosorbent assay) by Sun Long and Biotech company ELISA kit. The program of SPSS 20.0 has been used for all statistical analyses. Biochemical analyses have been achieved to evaluate the salivary and the serum parameters amounts for all substances in both groups.

Results:

The clinical data of 117 participants were divided into 45 healthy subjects and 72 advance breast cancer patients (4th stage) groups that were registered for two different samples (blood and saliva) in this revision. The results depicted in Fig. 1 are for blood parameters levels (serum and plasma), while salivary parameters levels are present in Fig. 2. The results demonstrated that the levels of blood and saliva samples of IL-12 (P<0.0001), IL-6 (P<0.0001), IL-4 (P<0.001), 8-OHdG (P<0.0001), 8-NG (P<0.001, and P<0.004), TNF (P<0.002, and P<0.001) and IFN-γ (P<0.0001) were significantly higher in breast cancer as compared with healthy subjects, whereas there were significant lowering (P<0.0001) in catalase activates in breast cancer in both samples as seen in Figs. 1 and 2. The results in Fig 3 are for salivary and serum MDA levels, it is shown that there is a significant rise in both samples (P<0.0001, and P<0.0002) in breast sarcoma patients when associated with control groups.
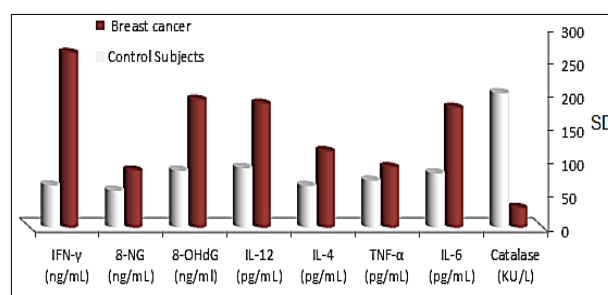
Figure 1. Catalase, IL-6, IL-4, IL-12, 8-OHdFG, 8-OH and IFN-γ levels in blood samples of healthy controls compared with breast cancer patients (Values are expressed in mean ± SD).

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Figure 2. Catalase, IL-6, IL-4, IL-12, 8-OHdFG, 8-OH and IFN-γ levels in salivary samples of healthy controls compared with breast cancer patients (Values are expressed in mean ± SD).
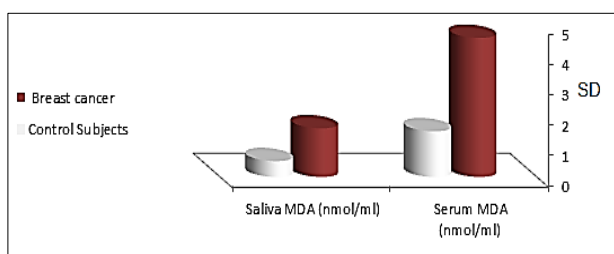
Figure 3. Salivary and serum MDA concentrations in healthy controls compared with breast cancer patients (Values are expressed in mean ± SD).

Discussion:

Cytokines are primarily designated as regulator of immune reply and inflammation. On the other hand, an improving number of papers have suggested the raises of some sorts of cytokines, which are linked with the initiation and advancement of carcinoma. Therefore, the starring role of the malignancy associated to cytokines has grabbed extensive consideration [19]. The cytokines that endorse carcinoma improvement are tangled in harmonized system. While the mechanisms prevailing some paths have been clarified by in vitro revisions or animal investigations, numerous cytokines were established to be raised up in patients with malignancy or tumor microenvironments [20-21], these bonds with our data showing significant increased levels of numerous cytokines levels of both blood and saliva samples in breast cancer as compared with healthy subjects such as: IL-12 ($P<0.0001$), IL-6 ($P<0.0001$), IL-4 ($P<0.001$), 8-OHdG ($P<0.0001$), TNF ($P<0.002$, and $P<0.001$) and IFN-γ ($P<0.0001$), these have been observed in Figures 1 and 2. Sánchez-Zauco et al showed that the blood amounts of IL-1β, IL-6, IFN-γ, and IL-10 were significantly developed in gastric carcinoma cases [22]. There were discovered significant rises in the blood samples (serum, plasma) concentrations of IL-4 among carcinomas cases in breast and pancreatic [23-24]. Hussein et al proved that serum levels of IL-6 and IL-12 are extremely raised in breast cancer patients and connected with carcinoma evolution [25]. IL-12 is central for the enrolment and influencing functions of CD8+ T and NK cells. Consequently, IL-12 is a chief provider to influence anti-growth immune replies [18] and this agreed with our results. Panis et al revealed the developed amount of TNF-α, IL-1β, IL-12, and IL-10, whereas there is a decline in catalase, 8-isoprostanes, and GSH levels as observed in breast carcinomas cases [26]. TNF-α is conceded one of the key intermediaries of sarcoma linked inflammation. It is tangled in the enrollment and variation of immune suppressor cells, prominent to ducking of tumor immune observation. In upraise amounts TNFα is capable of abolishing methylcolanthrene that encouraged malignancy [27]. Besides Greish et al detected that adding of TNF-α to doxorubicin in 4T1 tumor-bearing mice did not improve anticancer growing against 4T1 breast sarcoma in vitro [28]. Another study argued that the levels of IL-4 and IL-17 in blood serums had been improved significantly in patients having breast sarcomas, also the level of IFN-γ was raised in collections of breast malignancies when compared with benign breast tumor collections, on the other hand there were no significant difference between two collections [29]. All of the above research showed results which agree with this revision. AL-Musawi et al noticed that significantly raising of serum MDA, PC, 8-OHdG, IL-1β and Caspase-3 concentrations in breast sarcoma and nonthreatening breast tumor when compared to healthy subjects [30]. Verigos et al stated that elevated levels of serum 8-OHdG and 8-NG were observed during the course of irradiation in breast malignancy [14]. This is due to the formation of peroxynitrite form overproduction of nitric oxide, which caused the production of 8-NG, a marker of nitrative DNA harm. Alteration of 8-NG spontaneously to apurinic site is by merging adenine throughout DNA replication may cause mutation of G to T. Consequently 8-NG is a probable DNA mutagenic cut tangled in inflammation and malignancy refereed [31], and this is in agreement with this paper that raised blood and salivary levels of 8-NG ($P<0.001$, and $P<0.004$) significantly. Salman et al studied serum catalase activity and glutathione level in breast malignancy patients, which indicated that both markers reduced significantly [32]. As match of the current study that revealed significantly dropping ($P<0.0001$) in catalase activity in salivary and blood samples as apparent in Figures 1 and 2. This is perhaps due to diverse catalase transmutations in patients that can be the source of dwindled catalase levels triggering raise of hydrogen peroxide amounts in the blood

and tissues [33]. In contrast Hawang et al showed improved catalase expression in malignant tumor [34]. While Sawczuk et al observed no significant differences in salivary catalase activity, but clinically significant of salivary peroxidase, advanced glycation end-products, total antioxidant status, and MDA, perhaps these have certain clinical significance in un-invasive diagnostics of breast sarcoma [35]. Additional research explained that serum MAD level was developed in sarcoma patients (breast and colon cancer) [17]. The two papers before are similar to the current results displayed in Figure 3 for both salivary and serum MDA levels that were significantly higher (P<0.0001, and P<0.0002) in breast sarcoma patients when associated with control groups. Alongside the salivary cytokines level was raised such as in IL-2, IL-4, IL-6, IL-10 and, IL-18 except for IL-8 level reduced in breast malignancy and this is like the present outcomes manifested in Figure 2. At present, the vital mission is to seek for new biomarkers as a hopeful tool for early recognition and observing of breast carcinoma such as saliva [36]. Salivary indicators could be supportive to illustrate breast malignancy. There is narrow proof to authorize the putative implementation of salivary indicators as indicative tools for breast carcinogenesis at this time, so more investigations are needed [37]. Saliva can be a prized cradle for the detection of the oral and general diseases together [38-39].

Conclusions:

In this revision the following conclusion can be pinched from the study the levels of blood and saliva samples of MDA, IL-12, IL-6, IL-4, 8-OHdG, 8-NG, TNF and IFN-γ are significantly higher in breast cancer, whereas there was a significant lowering in catalase activates, so these parameters may be used as bio-indicator for early designates, because bio-indicator could be utilized as diagnostic tool in early stage (1) in breast cancer patient, exposure, medical conduct and severity of breast cancer. Thus larger investigations with higher number of participants are required to get representative results. The data of this article show that there is a direct positive correlation between the salivary and the serum bio-markers levels, which proves that the salivary non-invasive examination has a significant association with the serum investigation. The exchanging of blood to salivary components evaluation in this investigation may be utilized as a diagnostic tool. Accordingly, the salivary diagnosis embraces a non-invasive process and tumor progression in breast malignancy patients. Besides saliva may well signify as an active new gate as blood evaluation but easier and cheaper.

Author's declaration:

- Conflicts of Interest: None.
- I hereby confirm that all the Figures and Tables in the manuscript are mine. Besides, the Figures and images, which are not mine, have been given the permission for re-publication attached with the manuscript.
- Author sign on ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee in Hawler Medical University.

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مراجعة بعض المؤشرات الحيوية مع السيتوكينات في سرطان الثدي

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الخلاصة:

سرطان الثدي هو أكثر فئات السرطان التي يتم اكتشافها تكرارا والسبب الثاني للوفيات المرتبطة بالسرطان بين النساء في جميع أنحاء العالم. المؤشر الحيوي للورم هو مصطلح يستخدم لوصف المؤشرات المحتملة لتشخيص السرطان وتطوره وتقدمه.الهدف من هذه الدراسة هو تقييم جزء من بعض السيتوكينات و المؤشرات الحيوية لعينات المصل واللعاب في سرطان الثدي ثم تقدير قيمتها المحتملة في التشخيص المبكر لـ سرطان الثدي عن طريق إجراء المزيد من الأبحاث حول اللعاب، واستخدام اللعاب بدلاً من الدم (المصل والبلازما) في جمع عينات من المرضى. تم أخذ عينات المصل واللعاب من 72 مريض بسرطان الثدي و 45 من الضوابط السليمة ، من أجل التحقيق في السيتوكينات التالية مثل إنترلوكين 12 (IL-12) ، إنترلوكين 6 (IL-6) ، إنترلوكين 4 (IL-4) ، هايدروكسيغوانين (8-OHdG)، ومستويات عامل نخر الورم (TNF) و انترفيرن (IFN-γ) مع مؤشرات حيوية أخرى مثل مالونديالديهيد(MDA) ، الكاتلاز ، و 8 نيتروغوانين(8-NG) . أظهرت النتائج أن مستويات عينات الدم واللعاب من (P <0.0001) IL-12 ، IL-6 (P <0.0001)، IL-4 (P <0.001) ، 8-OHdG (P <0.0001)، 8- NG (P <0.001) ، و (P <0.004) ،و TNF (P <0.002) و (P <0.001) ، و IFN-γ (P <0.0001)كانت أعلى بشكل ملحوظ في سرطان الثدي ، بينما كان هناك انخفاض كبير (P <0.0001) في نشاط الكاتلاز في سرطان الثدي في كلتا العينتين بالمقارنة مع الأشخاص الأصحاء. يمكن استخدام مستويات تبادل اللعاب ومكونات الدم في هذا التحقيق كأداة تشخيصية ، وتعيين الجزء المحتمل من MDA و Catalase و cytokines باعتباره مادة كيميائية حيوية مهمة في سرطان الثدي. وفقًا لذلك ، يشمل التشخيص اللعابي عملية غير جراحية ، وقد يشير أيضًا إلى بديل جيد لتقييم في الدم و عندتطور الورم في مرضى سرطان الثدي .بجانب اللعاب قد يشير أيضًا إلى أنه بوابة جديدة نشطة كتقييم للدم ولكن أسهل وأرخص.

الكلمات المفتاحية: سرطان الثدي، الكاتلاز، السيتوكينات، مالونديالديهيد، 8 نيتروغوانين