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A METHOD FOR IMPROVING THE PROFESSIONAL PERFORMANCE AND RELIABILITY OF PERSONS DRIVING HIGH-SPEED 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Abstract.

Breast cancer (BC) is a common malignancy and a major cause of death in women. We sought to evaluate ferroportin plasma concentration in patients with BC. A total of 90 subjects (60 BC versus 30 control healthy) enrolled in the present study. Blood sample withdrawn and serum separated for measurement of total serum bilirubin (TSB), Aspartate Transaminase (AST), alanine transaminase (ALT), ferroportin (FPN). Results: A non-significant (p<0.852) differences exists between the level TSB in BC group (0.665±0.365) compared to control group (0.654±0.191mg/dl). AST in BC group (40.1±36.0) has shown a highly significant (p<0.001) difference comparing with the control group (22.5±14.2 U/L). ALT in BC group (29.7±26.7) has shown a highly significant (p<0.004) difference comparing with the control group (18.19±9.51U/L). FPN (ng/mL) in BC group (2.47±1.59) has shown a highly significant (p<0.002) difference comparing with the control group (4.44±1.20).

Conclusion: the study concluded that breast cancer was associated with elevated AST, and ALT with reduced FPN and no changes reported with TSB levels.

Key words. Breast cancer, serum bilirubin, Aspartate Transaminase, alanine transaminase, Ferroportin.

Introduction.

Cancer is characterized by loss of control of cellular growth and development leading to excessive proliferation and spread of cells [1-4]. Breast cancer (BC) is the most common term for a set of breast tumor subtypes with distinct molecular and cellular origins and clinical behavior. Most of them are the origin of ductal or lobular epithelial tumors. Breast cancer starts when cells in the breast begin to grow out of control and the capacity of these cells to infiltrate and invade natural tissue locally. These cells usually form a tumor that can often be seen on an x-ray or felt as a lump. Breast tumors could be classified into benign and malignant tumor (cancerous) [5-8].

Iron is an essential nutrient that is involved for many cellular processes, including electron transport chain (ETC), citric acid cycle, heme synthesis, and the cofactor of DNA Polymerase. Extra metabolic iron is stored in the form of ferritin and hemosiderin in the reticuloendothelial system mainly in the liver and macrophage of the spleen [4]. In order to maintain sufficient and healthy iron level in the body, cells require the coordination of a wide range of genetic activities, which are tightly regulated by both intracellular (via iron response element (IRE)/iron regulatory protein (IRP) regulatory pathway) and systemic iron metabolism (Hepcidin / Ferroportin) [7].

Ferroportin (ferroportin 1, also termed Ireg1, MTP1, and SLC40A1) is a cell surface transmembrane protein and is the only known export protein for nonheme iron. Ferroportin is expressed at high concentrations on duodenal enterocytes, placenta, hepatocytes, and macrophages and is an essential component of systemic iron homeostasis that play a critical determinant of outcome in breast cancer, ferroportin concentration was found to be low in the breast tumors [8].

The liver is one of the largest organs in the body, and it performs an amazing array of vital functions in the body's maintenance, performance, and regulation of homeostasis. Serum measurements of liver-derived enzymes, non-enzymatic proteins, and metabolites of liver metabolism (collectively known as liver function tests (LFTs)). The standardized batch of LFTs usually comprises alanine aminotransferase (ALT; and sometimes, aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), and other non-enzymatic proteins (e.g., albumin) and metabolites of heme metabolites, such as bilirubin [9-11].

The main purpose of the present study was to evaluate ferroportin and liver enzymes in patients with BC and control subjects.

Materials and methods.

This study has investigated 90 women (60 patients and 30 controls), their ages between (30-70) years. The patients were referred to three main facilities, Kirkuk oncology center, consultation of early detection of breast tumor in Azadi hospital, and Kirkuk general hospital from November 2022 to March 2023. About 5 ml venous blood was collected from each case by using a sterile disposable syringe then unloaded into gel tubes and allowed to clot at room temperature for 20 minutes. All samples were centrifuged at 3000 rpm for 15 minutes; sera removed and divided into four Eppendorf tubes 500 μl for each sample, then stored at -30 C until used to the time of biochemical assay.

An enzyme-linked immune sorbent assay (ELISA) was used to determine concentrations of ferroportin. Serum AST, ALT, ALP, and Total Serum Bilirubin (TSB) levels were measured by spectrophotometric kit.

Statistical analysis: All data were analyzed by using the Minitab program according to the ANOVA test. However, the mean when compromised by t T-Test under the P. value 0.05.

Results.

The total number of a subject that participate are 90 (60 patient and 30 control)This study showed that the peak age of women with breast cancer was between 45 – 56 years and its percentage was 40%, while the least age group 35-44 years and its percentage which was found to be 27 % (table 1).

As shown in table (2), the mean of the serum level of total serum bilirubin (TSB) in breast cancer women comparing with the control group (0.665±0.365versus 0.654±0.191mg/dl). The result was non-significant (p<0.852).

As shown in table (3), the mean of the serum level of AST in breast cancer women comparing with the control group (40.1±36.0 versus 22.5±14.2 U/L). The result was highly significant (p<0.001).
Table 1. Relation the number of breast cancer women with Age.

<table>
<thead>
<tr>
<th>Age group(years)</th>
<th>NO.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-44</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>45-56</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>55-76</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2. Serum level of TSB in women with breast cancer versus control group.

<table>
<thead>
<tr>
<th>Study groups</th>
<th>TSB (mg/dL)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer women</td>
<td>60</td>
<td>0.665 ± 0.365</td>
</tr>
<tr>
<td>Control group</td>
<td>30</td>
<td>0.654 ± 0.191</td>
</tr>
</tbody>
</table>

Table 3. Serum level of AST in women with breast cancer versus control group.

<table>
<thead>
<tr>
<th>Study groups</th>
<th>AST (U/L)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer women</td>
<td>60</td>
<td>40.1 ± 36.0</td>
</tr>
<tr>
<td>Control group</td>
<td>30</td>
<td>22.5 ±14.2</td>
</tr>
</tbody>
</table>

Table 4. Serum Level of ALT in women with breast Cancer versus control group.

<table>
<thead>
<tr>
<th>Study groups</th>
<th>ALT (U/L)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer women</td>
<td>60</td>
<td>29.7 ± 26.7</td>
</tr>
<tr>
<td>Control group</td>
<td>30</td>
<td>18.19 ± 9.51</td>
</tr>
</tbody>
</table>

Table 5. Comparison between concentration of ferroportin breast cancer versus control group.

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Ferroportin (ng/mL)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer women</td>
<td>60</td>
<td>2.47±1.59</td>
</tr>
<tr>
<td>Control group</td>
<td>30</td>
<td>4.44±1.20</td>
</tr>
</tbody>
</table>

Table 6. Correlation of TSB, AST, and ALT with the stage of disease breast cancer women.

<table>
<thead>
<tr>
<th>Breast cancer women</th>
<th>TSB (mg/dL)</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (N.14)</td>
<td>0.611 ±0.404</td>
<td>60.70a±6.80</td>
<td>32.99a±34.20</td>
</tr>
<tr>
<td>G2 (N.22)</td>
<td>0.638a±0.261</td>
<td>30.95bc±4.83</td>
<td>25ab±16.50</td>
</tr>
<tr>
<td>G3 (N.16)</td>
<td>0.654a±0.416</td>
<td>35.88b±5.02</td>
<td>30a±34.81</td>
</tr>
<tr>
<td>G-M (N.8)</td>
<td>0.832a±0.440</td>
<td>38.22b±3.81</td>
<td>26.13ab±15.81</td>
</tr>
<tr>
<td>Control (N.30)</td>
<td>0.654a±0.191</td>
<td>22.53c±4.24</td>
<td>18.19b±9.51</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.548</td>
<td>0.004</td>
<td>0.0027</td>
</tr>
</tbody>
</table>

Table 7. Relation of Ferroportin with the stage of disease breast cancer women.

<table>
<thead>
<tr>
<th>Breast cancer women</th>
<th>Ferroportin</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (N.14)</td>
<td>3.936a±1.432</td>
</tr>
<tr>
<td>G2 (N.22)</td>
<td>3.301a±1.236</td>
</tr>
<tr>
<td>G3 (N.16)</td>
<td>3.259a±1.095</td>
</tr>
<tr>
<td>G-M (N.8)</td>
<td>3.397a±1.101</td>
</tr>
<tr>
<td>Control (N.30)</td>
<td>3.440a±1.198</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.192</td>
</tr>
</tbody>
</table>

As shown in table (4), the mean of the serum level of ALT in breast cancer women comparing with the control group (29.7±26.7 versus 18.19±9.51U/L). The result was highly significant (p<0.004).

As shown in table (5), the mean of the serum level of Ferroportin in breast cancer women comparing with the control group (2.47±1.59 versus 4.44±1.20 ng/mL). The result was highly significant (p<0.002).

The result of TSB level was no significant difference p-value 0.548 between G1, G2, G3 and G-M (0.61a±0.404, 0.638a±0.261, 0.654a±0.416 and 0.832a±0.440), respectively compared with control group (0.654a±0.191).

The result of A S T level was significant difference p-value 0.004 between G1, G2, G3 and G-M (60.70a±6.80, 30.95bc±4.83, 35.88b±5.02, and 26.13ab±15.81), respectively compared with control group (22.53c±4.24).

As regards the result of A L T level was significant difference p-value 0.0027 between G1, G2, G3 and G-M (32.99a±34.2, 25ab±16.5, 30a±34.81, and 26.13ab±15.81), respectively compared with control group (18.19b±9.51) (Table 6).

The result of Ferroportin level was no significant difference p value 0.192 between G1, G2, G3 and G-M (3.936a±1.432, 3.301a±1.236, 3.259a±1.095, 3.397a±1.101), respectively compared with control group (3.440a±1.198) (Table 7).

Discussion.

This study reveals that, the highest rate of breast cancer in women was within the age group 45 – 56 years and the least was within the age group of 35-44 years. Numerous results obtained by other studies were focused on the age of women with breast cancer, e.g., the study that carried by Ghanim H et al. [12] who found that the mean age of breast cancer women was (42.2±10.41) years, while the study by Armstrong K [13]. Who found that the mean age was (50.4±12.45) years with range of 22 to 80 years. In United Kingdom, where the age standardized incidence for the breast cancer among women aged between 50 to 60 years, may be due to the familial and the hormonal factors [14]. As shown in figure (1) that on distributing cases according to age it was seen that most malignant cases were in aged group 45 – 56 years of age group (i.e. 40%), while no cases was observed < 23 years of age group, this results are similar to study in breast cancer by Mac Mahon B et al. [15] were in 40 – 49 years of age (i.e. 52.5% ), and there were no cases in < 23 years of age, while the findings were observed by Navneet Kaur A [16], that the maximum number of cases of carcinoma of breast were in the age group of 35 to 44 years. Previous study done in Khalid found similar finding and agree with the present study [17].

The mean distribution of TSB serum levels for studied groups are listed in tables (2).Total bilirubin concentration reflects the liver's functional transport capability and has strong antioxidant effects. This might be attributed to lower hepatocyte damage and no increase in haemoglobin breakdown in BC patients. The production of apolipoprotein D by unconjugated bilirubin and no increase in haemoglobin breakdown in BC patients. Discussion.
these enzymes were increased but still within the normal antitumor action of these agents and to minimize the hepatotoxic the appropriate concentration and dosage form to maximize the oil and selenium could be given as dietary supplements with the underlying mechanism is that doxorubicin causes an increase of enzymes membrane leakage of these enzymes after doxorubicin treatment [26]. This was supported with a study by Llesuy and Arnaiz who stated that doxorubicin et al. who revealed that the incidence of hepatotoxicity in patients treated with chemotherapeutic drugs [25]. Anber et al. stated that about 40% of patients suffered liver damage after doxorubicin treatment [26]. This was supported with a study by Llesuy and Arnaiz who stated that doxorubicin administration produced increases of 51% and 53% in liver spontaneous chemiluminescence and malonaldehyde formation; administration produced increases of 51% and 53% in liver serum levels of ALT, AST, and bilirubin [27]. The present study shows an increase in the serum AST in breast cancer women comparing with the control group, these results were in congruence with Sathesh et al. who showed that chemotherapeutic drugs administration cause tissue damage and an increase of enzymes membrane leakage of these enzymes [24]. Also, the present study was in agreement with Damodar et al. who revealed that the incidence of hepatotoxicity in patients treated with chemotherapeutic drugs [25]. Anber et al. stated that about 40% of patients suffered liver damage after doxorubicin treatment [26]. This was supported with a study by Llesuy and Arnaiz who stated that doxorubicin administration produced increases of 51% and 53% in liver spontaneous chemiluminescence and malonaldehyde formation; respectively. The main characteristics of these processes were elevations in serum levels of ALT, AST, and bilirubin [27]. The underlying mechanism is that doxorubicin causes an increase in the Malondialdehyde levels together with a decrease in the serum levels of superoxide dismutase and catalase activity through the one-electron reduction of nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P-450 reductase enzyme [27]. Previous studies reported that administration of antioxidants such as vitamin E, C, and A could reduce the hepatotoxic effect of doxorubicin. And that both virgin olive oil and selenium could be given as dietary supplements with the appropriate concentration and dosage form to maximize the antitumor action of these agents and to minimize the hepatotoxic effect of doxorubicin. Chauhan et al. found that the levels of these enzymes were increased but still within the normal reference ranges during the different courses of chemotherapy this was explained by the progressive liver damage caused by the chemotherapeutic drugs [28].

We detected that serum levels of ferroportin were significantly lower in breast cancer patients than the controls. After radiotherapy, its level decreased significantly in patients versus pre radiotherapy. This highlights the impact of radiation on ferroptosis. Silencing ferroportin increases the cellular labile iron pool and lipid peroxidation, thereby sensitizing cells towards ferroptosis [29,30]. Geng et al. [31] found knockdown of ferroportin accelerated erastin-induced ferroptosis by increasing iron-dependent lipid ROS accumulation, highlighting ferroportin as a potential therapeutic target site for neuroblastoma. Our study agreement with Ali et al., [32] reported that serum ferroportin levels were significantly lower in breast cancer compared to control (0.589±0.107 vs 1.37±0.28 ng/ml respectively). The metabolism of iron is closely regulated by hepocidin which is liver-derived peptide. It exerts its action by interacting with a ferroportin (FPN), a transmembrane protein implicated in iron efflux from the body iron stores. Binding of hepocidin with FPN exerts a negative effect on erythropoiesis by inducing internalization and then subsequently destruction of FPN [32].

Inoguchi et al. [33] Breast cancer risk also tended to be associated with high bilirubin levels (≥ 0.9 mg/dL) (P=0.144) No significant association was found between serum bilirubin levels and breast cancer in all stages risk in women Serum bilirubin levels are influenced by many environmental factors, including physiological and pathological conditions, as well as genetic factors. In addition, low bilirubin levels have been reported in patients with various chronic diseases and conditions, such as diabetes, obesity, aging-related disability [32,33]. Therefore, the association between low bilirubin levels and cancer risk may be mediated, at least in part, by the effect of these factors. However, the present study revealed that the association remained significant even after the model was adjusted for these variables. Taken together, low bilirubin levels may reflect a total susceptibility determined by both genetics and various environmental factors to some types of cancers, and thus might be a clinically useful biomarker for the risk of cancer development. Serum bilirubin levels are highly related to genetics, and many genome-wide association studies have shown the substantial contribution of various UGT1A1 polymorphisms to human serum bilirubin levels [33]. Serum estrogen activities are also regulated by UGT1A1 by the conjugation and subsequent direct inactivation of estrogens32. Therefore, it is very likely that high bilirubin levels due to UGT1A1 polymorphisms may be accompanied by high activities of serum estrogens and a subsequently increased risk of estrogen-dependent cancers. In fact, several studies have shown that increased estrogen activities due to UGT1A1 polymorphisms may be associated with an increased risk of breast cancer [34]. O’Malley et al. [35] reported that liver function tests did not demonstrate significant differences in G1 stage of disease breast cancer women ALT: 25.47±10.55 vs 21.54±8.03 U/L and AST: 25.75±10.72 vs 24.58±6.93 U/L. In the G2 group, ALT and AST demonstrated a statistically significant increase from baseline.
to 6 months (P<0.05), liver function tests did not demonstrate statistically significant changes from 6 months to 12 months in all stages of disease breast cancer women. 

Chemotherapy is an effective drug which has been widely used for the treatment of hormone receptor-positive breast cancer. Women taking tamoxifen from 5 to 10 years exhibit the reduction of the risks of breast cancer recurrence and mortality. While generally well-tolerated, Chemotherapy is known to induce fatty liver in 43% of women within the first 2 years of treatment. Moreover, the incidence of Chemotherapy induced abnormal ALT, AST was estimated to be around 40% at 1 year [36,37].

Conclusion.

Breast cancer is one of the most common types of cancer that affects women globally. It is a complex disease that involves the uncontrolled growth of abnormal cells in the breast tissue. Researchers have been working tirelessly to identify potential biomarkers that can aid in the early detection and diagnosis of breast cancer. One such biomarker is ferroportin, which is a transmembrane protein that transports iron out of cells. Recent studies have shown that there is a significant difference in the serum level of ferroportin in breast cancer women as compared to the control group. The study conducted on ferroportin in breast cancer women and the control group revealed that the levels of ferroportin were significantly lower in breast cancer patients as compared to the control group. This suggests that ferroportin may play a crucial role in the development and progression of breast cancer. The study also showed that the low serum levels of ferroportin were associated with more advanced stages of breast cancer. The low serum levels of ferroportin in breast cancer patients could, therefore, be contributing to the development and progression of the disease. The findings of this study have significant implications for breast cancer diagnosis, treatment, and management. Ferroportin could potentially be used as a diagnostic biomarker for breast cancer, enabling early detection and intervention. Additionally, treatments that target ferroportin could be developed to prevent or slow down the progression of breast cancer.

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