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Original Article

CHANGES IN SERUM ASCORBATE, URATE AND COPPER LEVELS IN WOMEN WITH CARCINOMA OF THE BREAST

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Abstract
Breast cancer is the most common malignancy among females. The pathogenesis of breast cancer is obscure but the major risk factors include age, family history and life style. In the present work, the relationship between breast cancer and changes in the levels of ascorbate, urate and copper at different clinical stages were studied. The results were compared with age and sex matched controls. The serum ascorbate levels were found to be decreased significantly in breast cancer patients from stage II to stage IV, whereas no significant change was observed in stage I. Serum urate levels were increased as the disease progresses from stage I to stage IV. Serum Copper levels were increased significantly in breast cancer patients from stage II to stage IV. Our results suggest that decreased ascorbate levels leads to higher oxidative stress, which may the cause of breast cancer. The elevated concentration of serum Uric acid level in breast cancer patients may be viewed as an index of increased antioxidant defense to compensate the loss of other antioxidant mechanisms. Furthermore, increased copper levels may induce DNA damage which may result in cancer.

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Key words: Ascorbate, Urate, Copper, Breast cancer

Introduction:
Carcinoma of the breast, the most common cancer in women, is the third most common cancer in the world, accounting for the highest morbidity and mortality in women (1). The exact cause of breast cancer is not completely known, but presumably it represents a complex interplay of genetic susceptibility and environmental factors (2). The role of antioxidant vitamins, diet and lifestyle modifications in modulating human cancer incidence have drawn significant attention from basic and clinical scientist. The issue has been critically reviewed with respect to cancer prevention (3). Epidemiological studies have revealed that low levels of essential antioxidants in circulation are associated with an increased risk of cancer (4). Ascorbic acid is a powerful antioxidant and can neutralize reactive oxygen metabolites and reduce oxidative DNA damage and genetic mutations (5). It has also been reported that ascorbic acid may enhance host immunologic functions (6). Epidemiologic studies have indicated an inverse association between vitamin C intake and the risk of cancer (7). Noroozi et al (8) were suggested that vitamin C readily scavenges reactive oxygen molecules (ROMs) and provide definite protection against oxidative DNA damage at normal physiologic concentration. Uric acid has been demonstrated to be an important antioxidant and a free radical scavenger in humans. It is one of the major radical trapping antioxidants in plasma and is reported to protect the erythrocyte membrane against lipid peroxidation (9). Urate also possesses antioxidant activity (10). In has been found to protect ascorbate against oxidation by cupric ion and iron induced oxidation (11). Uric acid interacts with peroxynitrite to form a stable nitric oxide donor, thus promoting vasodilatation and reducing the potential for peroxynitrite induced oxidative damage (12). Thus uric acid could be expected to protect against oxidative stresses. Reduction of H$_2$O$_2$ by copper ion produces highly reactive DNA damaging species (13). Copper ion induces significantly more DNA base damage in the presence of H$_2$O$_2$ than does ferrous ion (14,15), the other biologically relevant transition metal ion. For these reasons, there is an increased interest in the ability of copper ion to participate in DNA damaging reactions in vivo (16).

Methods:
Forty newly diagnosed breast cancer patients (ten at each stage), ranging in age from 32 to 65 years from Department of Oncology, Govt. General Hospital, Kurnool, Apollo Medical Centre, Kurnool (A branch of Apollo Hospitals, Hyderabad) and GowriGopal Hospitals, Kurnool, who had not undergone any previous treatment were chosen for this study. An equal number of age matched normal women served as control. Blood was obtained by venous puncture
in a sterile tube and was allowed to clot. Serum was separated by centrifugation at 1000g for 15 minutes. For plasma, blood was collected by venous arm puncture in a heparinised tube and plasma was separated by centrifugation at 1000g for 15 minutes. Blood samples obtained from breast cancer patients were analyzed together with an equal number of age and sex matched normal healthy subjects. Ascorbic acid was estimated by the method of Omaye et al (17). Uric acid was estimated by the method of Caraway (18). The copper content was estimated by sodium diethylthiocarbamate method (19). The data for biochemical analysis were expressed as mean ± S.D. t-test was applied to determine the significance of various biochemical changes among the clinical stages (I, II, III and IV) and controls.

Figure 1: Ascorbate and Urate levels at different clinical stages of breast cancer and in control

Table 1: Changes in the levels of Ascorbate, Uric acid and Copper in the serum of breast cancer patients at various stages and normal control (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control n=10</th>
<th>Total Breast Cancer Patients n=40</th>
<th>Breast cancer patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C (Mg/dl serum)</td>
<td>1.10 ± 0.39</td>
<td>0.82 ± 0.25</td>
<td>Stage-I n=10</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.92 ± 1.21</td>
<td>8.03 ± 0.75</td>
<td>Stage-II n=10</td>
</tr>
<tr>
<td>Copper</td>
<td>160.4 ± 6.1</td>
<td>198.2 ± 13.4</td>
<td>Stage-III n=10</td>
</tr>
</tbody>
</table>

a-significantly different from control (P<.05)

between vitamin C intake, mainly from fruit and vegetable and cancer (20). A multitude of epidemiologic studies have shown that increased consumption of fresh fruit and vegetables is associated with a reduced risk of most types of cancer (21). Of the hormone dependent cancers, only breast cancer was inversely associated with Vitamin C intake, in contrast with ovary and prostate cancers (21).

Reports of Thangaraju et al (22), and Manoharan et al (23), are in support of our present observation of decreased Vitamin C levels in breast cancer patients and intensification of Vitamin C deficiency as the disease advanced to stage III and IV. Lower concentration of Vitamin C may be one of the possible factors for higher plasma lipids, which modulate tumor cell proliferation. Since Vitamin C levels are decreased, they are likely not sufficient enough to counter ROMs attack thereby resulting in higher oxidative stress, which may be the cause of cellular and molecular damage thereby leading to cell proliferation and malignant conversion in the development of breast cancer. The significant decrease in vitamin C level at stage-III and its further intensification in stage-IV of breast cancer indicate the consequences of Vitamin C deficiency leading to cell proliferation and malignant conversion are intensified in stage-III & IV compared to stage I and II. Uric acid may appears to make a significant contribution to serum antioxidant capacity it has been found to stimulate granulocyte adherence to the endothelium (24), and peroxide and superoxide free radical liberation (25). Therefore, uric acid may have a deleterious effect on the endothelium through leukocyte activation and, interestingly, a consistent relationship and circulating inflammatory markers (26,27). The elevated concentration of serum Uric acid level in breast cancer patients may be viewed as an index of increased antioxidant defense to compensate the loss of other antioxidant mechanisms. In contrast to our results, Nagini et al (10) reported, decreased serum Uric acid levels in oral cancer patients. DNA damage induced by copper ion mediated reduction of H2O2 has been studied with respect to reaction, mechanism, reaction Kinetics (28), damage products (29) and DNA Sequence context effects (30). DNA damage induced by copper ion mediated reduction of H2O2 is site specific for instance, it occurs only at sites of DNA bound copper ion.

Results:
Table 1 shows the alterations in the levels of Vitamin C in all clinical stages of breast cancer and normal control. Vitamin C levels were found to be decreased in breast cancer patients, when compared to control. Vitamin C concentrations were decreased by 3.6% to 39% from stage-I to Stage-IV of cancer patients. A significant decrease was not observed in Stage-I, where as 24% decrease was observed in stage II and, 30.9% and 39% in stage-III and stage-IV respectively, when compared to control. Uric acid concentrations were found to be significantly increased in all clinical stages of breast cancer patients, when compared to controls. Serum Uric acid levels were increased by 16% to 45% as the disease progresses from stage - I to Stage - IV (16%, 39%, 41% and 45%), when compared to normal control.

In present study, serum copper levels were estimated among breast cancer patients in relation to different clinical stages and in normal subjects (Table 1). Serum copper levels were found to be increased significantly in stage - II, III and IV breast cancer patients, when compared with controls. But in stage - I patients the serum copper levels were not altered significantly. Markedly elevated serum copper levels (69.4%) were observed in stage - IV cancer patients, when compared to stage III (14%).

Discussion:
Epidemiologic studies have shown an inverse association
The kinetic data of goldstein and czapski (31), suggest that the sequence of events leading to DNA damage begins with reduction of cu(II) in solution. Free cu(I) is rapidly bound to DNA with high affinity (32). H2O2 then enters the coordination complex of DNA-cu(I), resulting in oxidation of cu(I) and DNA damage. Failed repair of damaged DNA and an inability to regulate an essential check points in cell cycle may result in cancer. Similar to our studies enhanced serum copper levels are reflected in oral cancer patients by observing enhanced plasma ceruloplasmin concentration in these patients (33). Regardless of the true reaction mechanism, exposure of DNA to copper ions has been reported to result in single and double stranded breaks, modified bases, abasic sites, and DNA protein cross links (34,35).

References:

27. crystal induced inflammation in man: a possible model to study the acute phase response. Ann Rheum Dis. 44: 533-536.


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