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Effect of serum magnesium, and copper in breast carcinoma patients: A comparative cross sectional study in tertiary care hospital, Madhya Pradesh, India

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Abstract---Background: In our country, there has been little study on breast cancer individuals during and progression of the cancer on magnesium, and copper have not been considered in existing studies. Aim: To determine the effect of serum magnesium, and copper in breast cancer subjects and to compare them with the apparently healthy controls. Methods: Lately diagnosed female subjects with breast cancer in the age group of 40-60 years were included in the study. Apparently healthy controls were selected from the group of people who were attending for annual health check-up and found to be healthy. Results: On comparison between the two groups, the present study observed that serum copper level was lower in case of apparently healthy controls than breast cancer subjects. Comparing between the groups of serum magnesium level, the present study observed significant difference. Similarly, the serum copper level was also found to be significantly differed when compared between the two groups. Conclusion: The altered values of magnesium and copper are

responsible for the initiation of breast cancer. In addition, present study implies that serum copper can be used as biomarkers for early identification and diagnosis of breast cancer.

Keywords---serum magnesium, serum copper, breast carcinoma, biomarkers.

Introduction

About 1 in 8 U.S. women (about 12%) will develop invasive breast cancer over the course of her lifetime[1]. In 2020, an estimated 276,480 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S., along with 48,530 new cases of non-invasive (in situ) breast cancer[2]. It is the most common female cancer in urban India 30 per 100,000 female population per year & 5 per 100,000 female population per year in rural areas[3].The five-year relative survival for women suffering from localized breast cancer is 99%, but women diagnosed with metastatic breast cancer disease have a five-year relative survival of only 27% [3].

Magnesium is essential for the activity of many enzymes[4]. Magnesium is a cofactor for more than 300 enzymes in the body; in addition, magnesium is allosteric activators of many enzyme systems[4]. The body contains about 25 g of magnesium, most of which (55%) is present in the bones in association with calcium and phosphorus, a small proportion of the body's content is in the Extracellular Fluid (ECF). Curiosity in the role of magnesium in medical research has been rising in recent decade. Cancer is a disease of alteration or failure of immune response. Magnesium seems to be essential for humans and various metabolic processes and immune responses are dependent on its normal concentrations. Magnesium deficiency has been implicated in various diseases including diabetes, anaemia, depression, ageing, low sexual potency and heart disease[5,6,7,8]. The interesting risk factor is magnesium bioavailability individuals. Considering the hypothesis of association of magnesium with cancer, literature demonstrates that during there is loss of magnesium[9,10]. The causes that could relate to this loss are frequent urination, insulin resistance, absorption, and deficient intake[4,9,10,11,12].

Copper is a vital trace metal that occurs in all body tissues. Copper is also essential for the formation of basement membrane ingredients including collagen formation. In addition, it is an important for a wide range of physiological functions including the production of red blood cells, maintenance of nerve cells, and most importantly regulation of immune cells. While leukocyte recruitment to the site takes place during and progression of cancer that plays a crucial role for the innate immune response, hence interest of copper in breast cancer increased. Studies across the globe have demonstrated higher copper levels in breast cancer subjects[13,14]. In another study[15] observed higher levels of copper in the serum of newly diagnosed subjects of breast cancer. Yucel et al., 1992, in their report demonstrated increase of copper levels in the subjects affected with breast cancer[16].

Materials and Methods

This study titled "Effect of Serum magnesium and copper in Breast Carcinoma Patients: A Comparative Cross Sectional Study in Tertiary Care Hospital, Madhya Pradesh, India" was carried out during the period of from January 2019 to January 2022.The study was conducted on 100 subjects admitted during the above period in research Centre of Index Medical College and Hospital, Indore, Madhya Pradesh, India affiliated to Malwanchal University with an aim to evaluate the effect of Serum magnesium and copper in breast carcinoma patients.

Inclusion Criteria

Lately diagnosed female subjects with breast cancer in the age group of 40-60 years attending to research Centre in Index Medical College and Hospital, Indore, Madya Pradesh, India affiliated to Malwanchal University were included in the study. These breast cancer subjects were chosen irrespective of type and stage of the pathology. Apparently healthy controls were selected from the group of people who were attending for annual health check-up and found to be healthy. These control subjects were eventually selected only when they cleared and notified by the attending physician of them to include in the control group. The age matched control subjects are selected from apparently healthy women attending for health check up in the research Centre in Index Medical College and Hospital.

Exclusion Criteria

The breast cancer group subjects or apparently healthy control group subjects suffering from co-morbid conditions which affect serum levels of oxidative stress markers and other malignancies, and those undergoing treatment for breast cancer were excluded from the study. Serum was separated and tests were performed according to standard procedure for each marker on the same day.

Ethics

This study was approved by the Institutional Ethics Committee of Index Medical College and Hospital, Indore, Madhya Pradesh, India affiliated to Malwanchal University. An informed written consent was taken from all the patients involved in the study after explaining regarding the study.

Study Procedure

Fasting venous blood (5ml) were drawn[27] into the plane vials, after informed written consent was taken from all the study group subjects. Serum was separated by centrifuging the blood at 3000 rpm for 20 minutes and stored in aliquots at -20^{o} C until assayed. Serum was processed to assess the levels of serum magnesium and copper.

Statistical analysis

SPSS statistical software was used to perform statistical analysis. Unpaired 't' test was performed to compare the means of variables between two groups.

Percentages were also calculated. Chi-Square test was used to check the relative risk & Odds ratio. P <0.05 was considered significant.

Sampling population

Sample size is calculated[17] on the basis of incidence of breast cancer individuals using the formula :
Where σ_1 = 2 units, σ_2 = 5 units, the SD of number of breast cancer individuals

- d = mean (σ_1, σ_2) the minimum mean difference consider to be clinically significant
- Type I error a = 5% corresponding to 95% confidence level
- Type II error β = 20% for detecting results with 80% power of study
- So the required sample size n = 50

Results

In the figure 1, we have shown the serum values of magnesium and Copper in both the groups of the present study. Interestingly, serum copper level was lower in case of apparently healthy controls than breast cancer subjects. Whereas serum magnesium level was found to be higher in case of apparently healthy controls than breast cancer subjects. Comparing between the groups of serum magnesium level, the present study observed significant difference. Similarly, the serum copper level was also found to be significantly differed when compared between the two groups.

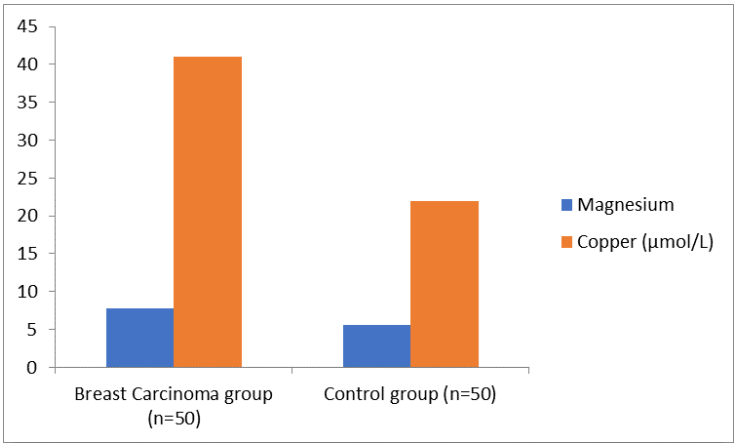

Figure 1. Bar diagram depicting the serum magnesium and copper values in both groups

A chi-square test of independence showed that there was no significant association between serum magnesium and breast cancer, X^2 (1, N = 50) = 0.7, p = .41. Similarly, the presence of breast cancer did not differ by the magnesium levels of breast carcinoma patients, X^2 (1, N = 50) = 0.1, p = .12. On the contrary, the serum magnesium are more likely to be associated with healthy nature of the control subjects X^2 (1, N = 50) = 10.7, p < .01.

A chi-square test of independence was performed to examine the relation between copper and the breast cancer subjects levels. The relation between copper levels and breast cancer were significant, X^2 (1, N = 50) = 7.9, p = .004. Serum copper level is more likely to highly express in the subjects affected with breast carcinoma. When performed a chi-square test of independence to examine the relation between reduced glutathione and the serum copper level in breast carcinoma. The relation between reduced glutathione and the serum copper level was significant, X^2 (1, N = 50) = 18.25, p = .0001. Reduced glutathione is more likely to less express in patients affected with breast carcinoma. The expression of reduced glutathione and the serum copper level did not differ in healthy control subjects, X^2 (1, N = 50) = 3.2, p = .19.

Figure 2 show the relationship of parameters in the present study group subjects. Pertaining to breast cancer group subjects, a negative correlation (y = -0.034x + 7.259 & R^2=0.033) between serum copper (x axis) with reduced glutathione (y axis) was established as evident from the graph shown in the figure 2.

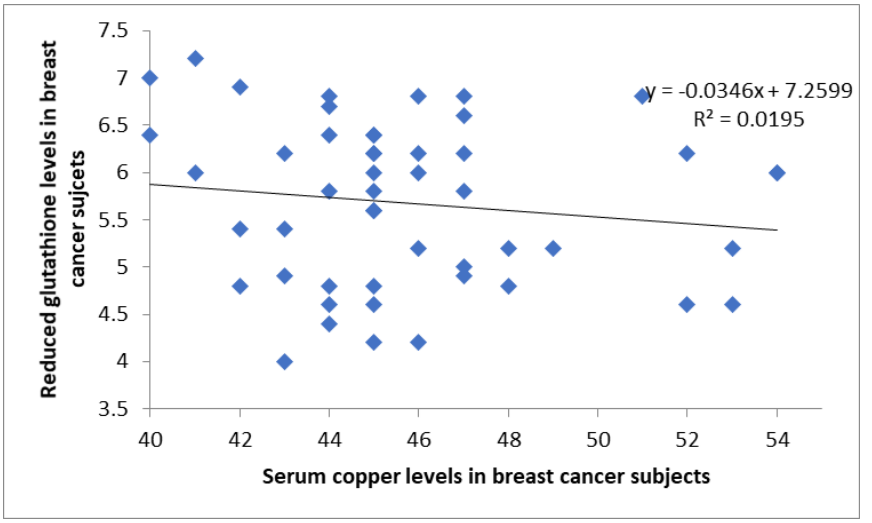

Figure 2. Scatter diagram showing relationship between serum copper & reduced glutathione in breast cancer group

Discussion

In the present study, lower serum level of magnesium was observed in the breast cancer subjects compared to the non-breast cancer (controls) subject population of the study. There is little information available on the internet with regards to magnesium concentration in breast cancer individuals across the globe. Therefore, the mechanism responsible for low magnesium level in patients with breast cancer is not completely known. Confining to the present study results, we infer that breast cancer is a disease in which there is excessive tumor cells production. With respect to that, glucose is the main source of energy to the cells, and more importantly, magnesium is very much needed for the oxidation of glucose to provide energy. Thus, we imply deficiency of magnesium is due to the fact of more consumption from the magnesium stores in the body and deficient replenish of magnesium stores. The other reason for low magnesium levels is that

re-absorption of magnesium takes place in the renal tubules, and for this insulin sensitivity is essential.

Similarly one report by Mora-Pinzon et al., 2018, have demonstrated in a cross-sectional study that higher levels of urinary magnesium were associated with greater breast density. This may be due to the lack of sufficient magnesium that affects the insulin action and also insulin sensitivity, thus the re-absorption in the renal tubules is impaired. On the other hand, reports does exist on the treatment of breast cancer individuals with relation to administration of magnesium salts to the same[18,19,20,21,22] . In addition, these reports[18,19] have also found that administering magnesium salts have attenuated the disease symptoms to some extent. Report by[23] Sartori et al 1992., have demonstrated that the increase intake of magnesium persists in actual by the tumor tissue. However, the clinical significance and evaluation at a cellular and molecular level of magnesium in regard to breast cancer remains unaddressed[19,23]. Magnesium is a mineral that participates in the metabolism of various nutrients and nucleic acids. In the presence of breast cancer, neoplastic cells increase the expression of magnesium transport channels, which raises the intracellular concentration of the mineral, contributing to tumor growth through its function of increasing energy demand[24,25].

Copper is a vital trace metal that occurs in all body tissues. It is an important for a wide range of physiological functions including the production of red blood cells, maintenance of nerve cells, and most importantly regulation of immune cells. Copper is also essential for the formation of basement membrane ingredients including collagen formation. Studies across the globe have demonstrated higher copper levels in breast cancer subjects[13,14]. In another study by[15] Pavithra et al., 2015, observed higher levels of copper in the serum of newly diagnosed subjects of breast cancer. Yucel et al., 1992, in their[16] report demonstrated increase of copper levels in the subjects affected with breast cancer. This report was conducted on newly diagnosed breast cancer subjects and compared against the healthy controls of same age as that of cases group. In addition, study by Gupta et al 1991, have observed higher levels of copper[26] in breast cancer subjects than benign breast diseases than healthy controls. Similarly, the present study also observed increased levels of copper in breast cancer subjects than apparently healthy controls. In addition, the present study also have the association of magnesium and copper levels in breast cancer subjects. Hence, the present study infers that the increase in the copper level is an indication due to the pathology of breast cancer.

Conclusion

From the results it can be concluded that altered values of magnesium and copper are responsible for the initiation of breast cancer. In addition, present study implies that serum copper can be used as biomarkers for early identification and diagnosis of breast cancer. Promoting this area of research through in-vitro and in-vivo studies will help to understand mechanistic insights that may ultimately guide clinicians in controlling breast cancer pathogenesis and also initiation and progression of the disease as well.The present study has also demonstrated that in patients with breast cancer, any innate natural

compensation mechanism may become insufficient to suffice the patho-physiological alterations, but it has not been extensively studied.

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