

SIGNIFICANCE OF SERUM COPPER AND ZINC LEVEL IN GASTROINTESTINAL CANCERPrathibha Yadav¹, Vishnu Datt Bohra²¹Associate Professor, Department of Biochemistry, Jaipur National Institute for Medical Sciences & Research Centre, Jaipur, Rajasthan.²Professor & HOD, Department of Biochemistry, Medical College, Jhalawar, Rajasthan.**ABSTRACT**

The roles of trace elements especially copper and zinc in carcinogenesis in relation to disease activity have shown useful in estimating the extent and prognosis of malignant tumor in the digestive organ. Keeping this in consideration, the study was conducted on 140 subjects either sex out of which 35 normal adults and 105 gastrointestinal (GI) cancer patients. The follow up study was further undertaken and values of serum Cu and Zn of the same patients before and after surgery were recorded. The study showed that there was significant elevation ($p < 0.01$) of serum copper levels before surgery and serum copper levels were decreased significantly ($p < 0.05$) after surgery. Serum Zn level was found significantly ($p < 0.05$) lower in GI cancer patients while the Zn level was increased significantly ($p < 0.01$) after surgery. There was significant increase ($p < 0.01$) in Cu/ Zn ratio of GI cancer patients before surgery in contrast to the control. The serum copper level in patients of GI cancer decreased significantly after surgery resulting normalization of metabolic process. A significant increase in serum Zn levels have been observed after treatment of the patients. The Cu/ Zn ratio decreased significantly after the surgery. These observations clearly indicate that serum Cu, Zn and Cu/ Zn ratio are useful in estimating the extent and prognosis of malignant tumors in digestive organs.

KEYWORDS

Copper, Zinc Gastrointestinal cancer, Malignancy.

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INTRODUCTION: Cancer is a the second largest killer disease after coronary heart disease in the developing countries⁽¹⁾ and leading cause of deaths worldwide. Cancer of gastrointestinal tract is one of the common malignancies in the United State, United Kingdom, Japan and Soviet Union.⁽²⁾ In India, gastrointestinal group cancer is the third largest group of cancer.⁽³⁾ They categorized 28.70 per cent uro-genital, 28.37 per cent oral pharyngeal and laryngeal and 13.31 per cent gastrointestinal cancer. Sabharwal et al.⁽⁴⁾ recorded the percentage incidence of malignant tumours in various parts of the gastro intestinal tract. They concluded that rectum and anal were the most susceptible sides with 28.28 per cent incidence of cancerous tumour followed by colon and oesophagus each with 25.25 per cent malignancy. Whereas, stomach and small intestine were comparatively less affected sharing 7.07 and 5.05 per cent incidence. Age and sex play an important role in gastro intestinal malignancy. Prabhakar et al.⁽⁵⁾ and Sharma et al.⁽³⁾ estimated 70 to 80 per cent gastro intestinal tract are susceptible to cancer in 40 per cent population age group varying between 30 to 60 years.

Several studies have shown that plasma copper concentrations are increased in various carcinomas. Zinc acts as a cellular growth protector, including growth of neoplastic cells, and its deficiency was demonstrated to be involved in several stages of malignant transformation.

However, the usefulness of the serum zinc and copper levels in cancer prevention, detection, monitoring treatment, and prognosis requires further investigations. Inutsuka et al.⁽⁶⁾ observed that the increase of plasma copper level (PCL) and decrease of plasma zinc level (PZL) neoplastic diseases particularly carcinoma of digestive organs. Further, they indicated that the ratio of PCL and PZL had more remarkable changes. The copper zinc ratio is useful in estimating the extent and prognosis of malignant tumour in the digestive organ. Trace elements like zinc, copper, iron and magnesium are known to be affected or affect various enzyme systems of the body directly or indirectly concerned with various metabolic and immunological mechanisms during different types of malignancy.⁽⁷⁾ High levels of copper and low zinc levels have been reported in gastrointestinal malignancy.⁽⁸⁻¹¹⁾

Keeping this in view the present study was under taken to determine the quantitative value and sensitivity of biochemical parameters applicable to find out malignancy in gastrointestinal tract namely oesophagus, stomach and colon. The study was under taken to compare the serum copper and zinc levels in patients with cancer of the gastrointestinal tract (oesophagus, stomach and colon) with normal subjects and variation of serum Zn, Cu levels and Cu/ Zn ratio after surgery.

MATERIAL AND METHODS: This study was carried out in Department of Biochemistry at SMS, Medical College Jaipur. Patient blood samples were collected from Gastro logy and Surgery Department of SMS, Hospital Jaipur. The study population included 140 subjects either sex was under taken of which 35 normal adults were having no symptoms of any disease and the rest 105 gastrointestinal cancer patients

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were the patients admitted in the wards of Gastrology and Surgery Departments. Of these there were 37, 30 and 38 patients distinguish had oesophagus, stomach and colon cancer respectively. At the time of their admissions the patients were found suffering from different types of GI malignancy as evidence by clinical as well as histopathological observation. 80 patients did not find their treatments continuously for various reasons. In fact only 25 patients remained for follow up studies as schedule for their complete treatments.

Fasting blood samples were collected from anti-cubical vein of healthy control and gastro intestinal cancer patients before and after surgery in plain vials. The blood was allowed to clot at room temperature and serum was separated after centrifuging. The serum samples were stored at -20°C until analysis.

The serum copper and zinc were estimated by using Atomic absorption Spectrophotometer, Model AA- 6300 of Shimadzu Corporation, Japan in the Research Centre for Livestock Health and Production, Durgapura, Jaipur. Atomic absorption spectrophotometry determines the sample by using the fact that sample concentrations are proportional to light absorbance in the atomization stage. Calibration curve method was used as the determination method. In this method different standards of known concentration were measured and the calibration curve of concentration verses absorption was prepared. The absorbance of the unknown sample was measured and the concentration of the target sample can be determined by using the calibration curve. Computer data system draws the curve and read the concentration automatically. Statistical significance was tested by student's t –test and paired t –test. $P < 0.05$ and

$P < 0.01$ were considered significant highly significant respectively.

RESULTS: The mean value of serum copper level of gastrointestinal (GI) malignant patients and normal subject are presented in Table 1. The mean value of serum copper is 88.73 µg/dl in normal subjects whereas in oesophagus, stomach and colon cancer patients these values are 196.78, 199.96 and 204.05 µg/dl. The serum copper level increased significantly ($p < 0.01$) in gastro intestinal cancer patients as compared to normal subjects. Higher elevation of serum copper in gastric malignancy than normal control group can be seen in Fig. 1.

It is clear from the table that serum copper levels of GI cancer patients reduced significantly ($p < 0.01$) and tend towards normalcy after their treatments. Figure 2 depicts declination in serum copper levels in GI cancer patients after their treatments. Mean values of serum zinc level of normal control subjects and patients suffering from GI cancer are presented in Table 3. The mean serum zinc value is 79.72 µg/dl in normal subjects whereas in oesophagus, stomach and colon cancer patients these values are 77.64, 76.29 and 77.37 µg/dl respectively. It can be noted that serum zinc level decreased significantly ($p < 0.05$) in GI cancer patients as compared to normal subjects. Declination of serum zinc in Gastric malignancy as compared to normal subjects can be seen in figure 1. Serum zinc levels before and after treatment of GI cancer patients are presented in Table 4. Data relating to follow up study revealed that zinc level of GI cancer patients increased significantly ($p < 0.01$) and tend towards normalcy. Elevation of zinc in different GI cancer patients after their treatments is shown in Fig. 2.

| Sl. No. | Subject | No. of cases | Mean±SE (µg/dl) | Range µg/dl | | CI (p = 0.01) µg/dl | | Compared to normal | |
|---------|-------------------|--------------|-----------------|-------------|-------|---------------------|-------|--------------------|---------|
| | | | | Min. | Max. | Lower | upper | t-test | p-value |
| 1 | Normal (control) | 35 | 88.73±1.42 | 75.1 | 110.5 | 86.90 | 91.55 | - | - |
| 2 | Oesophagus cancer | 37 | 196.78±2.94 | 165.0 | 250.0 | 192.99 | 200.5 | 32.48 | < 0.01 |
| 3 | Stomach cancer | 30 | 199.96±2.61 | 170.2 | 232.4 | 196.59 | 203.3 | 38.84 | < 0.01 |
| 4 | Colon Cancer | 38 | 204.05±2.95 | 172.1 | 242.5 | 200.24 | 207.4 | 34.31 | < 0.01 |

Table 1: Serum copper levels in normal (control) and gastro intestinal cancer patients

| Sl. No. | Subject | No. of cases | Serum Copper | | Paired t-value | p-value |
|---------|-------------------|--------------|------------------|-----------------|----------------|---------|
| | | | Before treatment | After treatment | | |
| | | | Mean±SE | Mean ±SE | | |
| 1. | Normal | 35 | 88.73±1.42 | - | - | - |
| 2. | Oesophagus cancer | 8 | 201.88±5.42 | 180.09±9.06 | 2.110 | 0.036 |
| 3. | Stomach Cancer | 7 | 197±3.83 | 165.83±7.47 | 3.767 | 0.046 |
| 4. | Colon Cancer | 10 | 210.06±7.36 | 160.76±11.60 | 10.006 | <0.01 |

Table 2: Serum copper levels in GI cancer patients before and after treatment

| Sl. No. | Subjects | No. of cases | Mean±SE (µg/dl) | Range (µg/dl) | | CI(p=0.01) (µg/dl) | | Compared to Normal | |
|---------|-------------------|--------------|-----------------|---------------|-------|--------------------|-------|--------------------|---------|
| | | | | Min. | Max. | Lower | Upper | t-stat | p-value |
| 1. | Normal (Control) | 35 | 79.72±1.73 | 70.00 | 105.0 | 76.72 | 81.17 | - | - |
| 2. | Oesophagus cancer | 37 | 77.64±1.36 | 65.00 | 92.20 | 75.89 | 79.39 | 2.539 | 0.0482 |
| 3. | Stomach Cancer | 30 | 76.29 ±1.42 | 65.12 | 89.07 | 78.21 | 81.88 | 2.482 | 0.0395 |
| 4. | Colon Cancer | 38 | 77.37 ± 0.93 | 68.00 | 89.10 | 76.17 | 78.57 | 2.821 | 0.442 |

Table 3: Serum Zinc levels in normal (control) and gastro intestinal cancer patients

| Sl. No. | Subjects | No. of cases | Zinc (µg/dl) | | Paired t-Stat | p-value |
|---------|-------------------|--------------|------------------|-----------------|---------------|---------|
| | | | Before treatment | After treatment | | |
| | | | Mean±SE | Mean±SE | | |
| 1. | Normal (Control) | 35 | 79.72±1.73 | - | - | - |
| 2. | Oesophagus cancer | 8 | 70.30±1.86 | 76.73±1.98 | 8.917 | <0.01 |
| 3. | Stomach Cancer | 7 | 69.90±3.58 | 76.74±6.25 | 5.594 | <0.01 |
| 4. | Colon cancer | 10 | 72.46±1.85 | 76.60±4.99 | 4.783 | <0.01 |

Table 4: Serum zinc level in Gastro-intestinal cancer patients before and after treatments

| Sl. No. | Subjects | No. of cases | Mean±SE | Range | | CI(p=0.01) | | Compared to normal | |
|---------|-------------------|--------------|------------|-------|------|------------|-------|--------------------|---------|
| | | | | Min. | Max. | Lower | Upper | t-stat | P-value |
| 1. | Normal (control) | 35 | 1.12±0.019 | 0.77 | 1.32 | 1.11 | 1.15 | - | - |
| 2. | Oesophagus Cancer | 37 | 2.56±0.047 | 1.82 | 2.92 | 2.49 | 2.66 | 27.71 | < 0.01 |
| 3. | Stomach cancer | 30 | 2.64±0.069 | 2.11 | 3.23 | 2.44 | 2.61 | 20.98 | < 0.01 |
| 4. | Colon Cancer | 38 | 2.65±0.045 | 2.15 | 3.21 | 2.59 | 2.70 | 29.96 | < 0.01 |

Table 5: Serum copper zinc ratio in normal (control) and gastro intestinal cancer patients

Table 5 exhibits serum Cu/Zn ratio of normal subjects and GI cancer patients. The mean value of serum of Cu/Zn ratio in normal cases is 1.12 whereas in case of oesophagus, stomach and colon cancer patients these values are 2.88, 2.83 and 2.90 respectively. It can be seen in the table that there is highly significant ($p<0.01$) increase in copper zinc ratio in different GI cancer patients as compared to control group. Serum copper zinc ratio levels before and after treatment of GI cancer patients are presented in table 6. It is apparent from the table that copper zinc ratio of GI cancer patients decreased significantly ($p<0.01$) after their treatments and tend toward normalcy.

| Sl. No. | Subjects | No. of Cases | Cu/Zn Ratio | | Paired t- Stat. | p-value |
|---------|-------------------|--------------|------------------|-----------------|-----------------|---------|
| | | | Before treatment | After Treatment | | |
| | | | Mean ±SE | Mean ±SE | | |
| 1. | Normal (Control) | 35 | 1.12 ±0.019 | - | - | - |
| 2. | Oesophagus Cancer | 8 | 2.88±0.17 | 2.36±0.08 | 3.824 | 0.049 |
| 3. | Stomach cancer | 7 | 2.83±0.17 | 2.16±0.21 | 3.981 | 0.036 |
| 4. | Colon Cancer | 10 | 2.90±0.10 | 2.30 ±0.14 | 3.951 | 0.038 |

Table 6: Serum copper/Zinc ratio in gastro-intestinal cancer patients before and after treatments

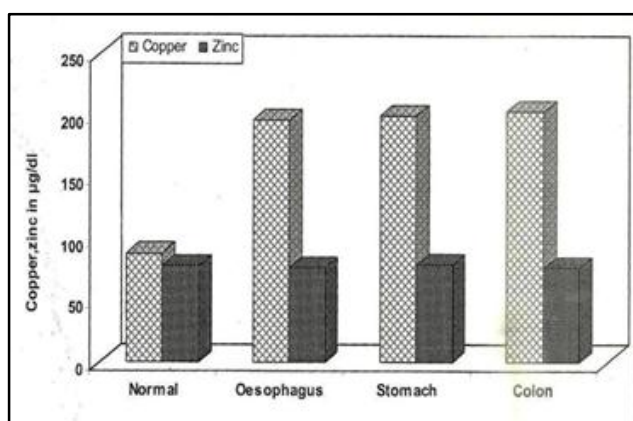


Fig. 1: Serum Cu and Zn in normal subjects and GI cancer patients

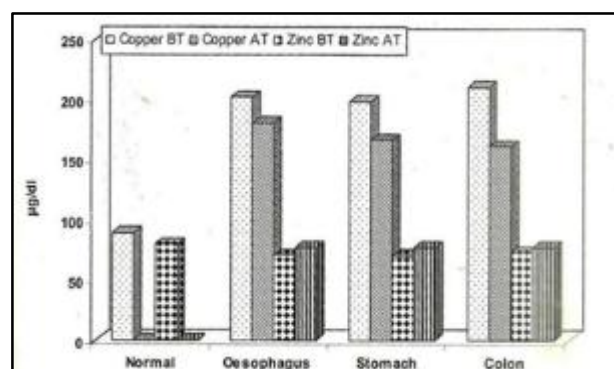


Fig. 2: Serum Cu and Zn levels before and after treatments in different GI cancer patients

DISCUSSION: Trace elements like copper and zinc are biologically essential for normal development, growth and function. It is very important to know their clinical significance, diagnostic and prognostic value in malignant diseases. The showed significant elevation ($p<0.01$) of serum copper level while there was a significant decrease in serum Zn level ($p<0.05$). Obviously there was A significant increase ($p<0.01$) of Cu/ Zn ratio of GI cancer patients in contrast to the control. Increase in levels of serum Cu of GI cancer patients may be due to destruction and necrosis of the malignant tissue leading to release of Cu stored within the cells into circulation or it may be the result of a non-specific acute phase reaction. Similar results in different malignancies have been reported by Cohen et al.⁽¹²⁾ and Vashney and Nizamuddin.⁽¹³⁾

The serum Cu levels in patient of GI cancer decreased significantly ($p<0.05$) after treatment and tend toward normalcy. This might be due to improvement of disease by treatment resulting normalization of metabolic process.

The relative decrease in Zn with increasing clinical involvement can be accounted for tissue catabolism. Zn is known to be a physiological antagonist of Cu and this may be responsible for hypozincemia observed with hypercupremia in malignant process. A significant ($p<0.05$) increase in serum Zn levels have been observed after treatment.

As the Cu level increased and the Zn level decreased the Cu/ Zn ratio increased significantly. In fact the use of ratio can be one of the important tools in diagnosis of cancerous patients more accurately than by the Cu or Zn level alone. The ratio increased gradually as the cancer advanced. The Cu/ Zn ratio decreased significantly ($p<0.01$) after the treatments.

CONCLUSION: These findings indicate that serum copper levels can be used to evaluate the progression of cancer, response to therapy and predict relapse, whereas serum zinc levels directly relate to the extent of disease.⁽¹⁴⁾ The significant marker was found to ratio of Cu/ Zn associated with the disease activity, response to therapy and predicting the relapse.

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