Non-Dialyzable Manganese and Copper Levels in Serum of Patients with Various Diseases\textsuperscript{1,2}

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Metabolism of copper and its relationship to disease was amply reviewed by Lahey et al (1), and by Adelstein and Vallee (2,3). In contrast to copper, reports on manganese are relatively few (4-11), and relationship to diseases has not been adequately explored.

The purpose of this paper is to compare non-dialyzable levels of copper and manganese in the blood serum of patients with various diseases to the levels observed in normal subjects.

\textbf{METHODS AND MATERIAL}

Fasting blood samples were collected from 236 hospitalized adult male subjects. Diagnosis and the number of subjects in each category were as follows: carcinoma of the prostate, metastatic, 7; leukemia, 5; cirrhosis of the liver, 5; Parkinson's disease, 8; multiple sclerosis, 14; diabetes mellitus, 58; azotemia, 102. Concurrently with these collections, blood leukocyte counts were made on patients with leukemia, serum acid phosphatase determinations (Bodansky method) were performed on patients with carcinoma of the prostate, serum glucose analysis were made on subjects with diabetes mellitus and urea nitrogen assays were made on serum of subjects with renal diseases.

Serum was separated immediately after clot formation. One ml aliquots of non-hemolyzed serum were dialyzed and activated in the CP5 Reactor, Argonne National Laboratory. The irradiation time was 30 minutes at a flux of $2.5 \times 10^{12}$ neutrons/cm$^2$/second. Samples were counted approximately one hour after irradiation over a 3 x 3 inch NaI crystal using a 512 channel (RCL) analyzer. This technique has been adequately described in our earlier publication (8).

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\textsuperscript{2}From the Radioisotope Research Service, Veterans Administration Hospital, Hines, Illinois, and Loyola University Stritch School of Medicine, Chicago, Illinois.
RESULTS

The summary of results obtained for all the subjects studied are presented in Table I and graphically illustrated in Figures 1 and 2.

Statistically significant elevations of manganese were noted in all the groups studied with the exception of patients with leukemia and carcinoma of the prostate. Increased copper levels were noted in patients with myocardial infarction and in patients with the carcinoma of the prostate while on estrogen therapy.

The data of patients with diabetes mellitus were grouped in a separate table (II) for the purpose of relating glucose concentrations to copper and manganese levels. Statistical evaluation of this data indicated that no relationship existed between the glucose levels and manganese concentrations. A highly significant relationship was present between the glucose and copper concentrations with p value between 0.001 and 0.005. The method of least squares (y = ax + b) produced the following equation:

\[ y = 0.149x + 102.9 \]

![Fig. 1. Scattergram of serum copper levels obtained from patients with various diseases.](image)

Key:  
I  Myocardial infarction  
II  Leukemia  
III  Cirrhosis of the liver  
IV  Carcinoma of the prostate  
V  Parkinson's disease  
VI  Multiple sclerosis  
VII  Diabetes mellitus  
VIII  Azotemia
where $y =$ copper concentration in $\mu g$ per 100 ml serum at a given glucose concentration ($x$) in terms of mgs per 100 ml serum.

The data of subjects with azotemia were also grouped in a separate table (III) for the purpose of relating the urea nitrogen levels to copper and manganese concentrations. Statistical evaluation of this data indicated that no relationship was present.

**DISCUSSION**

Serum copper data obtained in this study is in general accord with published results on the relationship of copper to disease (3,12,13). One major disagreement does exist with respect to results obtained on patients with diabetes mellitus. Kosenko (10) reported copper levels in 122 subjects with this disease to be about one-half the concentration noted in normal subjects. While copper concentration obtained in the present study is within the copper levels noted in normal subjects, the serum copper level is directly proportional to the glucose concentration in these subjects. The high correlation coefficient, 0.355, indicates that this relationship is real. Implications of this relationship may be numerous and only further studies can indicate its real significance.

Rechenberger (14) who studied serum copper in patients with nephrosis, concluded that the serum copper decreases and urine copper increases in direct proportion to the protein in the urine. The present study does not include the copper in the urine of these patients, hence direct comparison is not possible. About 15% of the subjects in the present group had serum copper levels which were greater than 200 $\mu g$ per 100 ml, while 11% of subjects had copper levels below 100 $\mu g$ per 100 ml. A study of clinical charts of patients with nephrosis did not reveal any clear-cut relationships with respect to copper concentration.

Patients with carcinoma of the prostate did have elevated serum copper levels (Table I and Figure 1). These high levels are attributed to the estrogen effect (2,3), since all these patients were receiving stilbesterol. Cherry et al (15) studied eight subjects with leukemia and reported that the periods of elevated leukocytes were associated with periods of hypercupremia. During the terminal stages of four of these subjects, the tendency of hypercupremia was reversed. The copper levels observed in the present study in patients with leukemia, none of whom were considered as terminal, are not considered significantly elevated above the normal levels or related to the white cell counts obtained.

Manganese levels have been reported to be elevated in serum of patients with myocardial infarction (7), and in patients with arteriosclerosis (9). The data presented in this study is in agreement with those reports. Kosenko (10) who studied trace elements in the blood of patients with diabetes mellitus, reported manganese levels to be about one-half of the normal levels. Lisun-Lobanova (16) also studied manganese in patients with diabetes mellitus, and reported that manganese had a tendency to be elevated in patients over 40 years of age and especially those between 61 and 70 years. The data presented in this study (Table I, Figure 2) reveal that elevated manganese levels, above 1.6 $\mu g$ per 100 ml, were noted in 62% of subjects with diabetes mellitus, and in 45% of
subjects with azotemia. Manganese levels below 1.0 μg per 100 ml were observed in 7% of patients with diabetes and in 11% of patients with azotemia. No statistical relationship of manganese to glucose or urea nitrogen concentrations was observed.

Increase in serum manganese levels appears to be present also in patients with multiple sclerosis and in patients with cirrhosis of the liver (Table II, Figure 2), although larger sampling would be desired. It may be noted that increased excretion of manganese in the urine of a patient with cirrhosis of the liver has been previously reported (17).

SUMMARY

Serum non-dialyzable copper and manganese levels were established in 236 hospitalized adult male subjects and compared with those obtained in 41

Fig. 2. Scattergram of serum manganese levels obtained from patients with various diseases.

Key:  I  Myocardial infarction
      II  Leukemia
      III  Cirrhosis of the liver
      IV  Carcinoma of the prostate
      V  Parkinson's disease
      VI  Multiple sclerosis
      VII  Diabetes mellitus
      VIII  Azotemia
apparently normal subjects. The disease category of patients included the following: leukemia (5), cirrhosis of the liver (5), carcinoma of the prostate (7), Parkinson's disease (8), multiple sclerosis (14), myocardial infarction (37), diabetes mellitus (58), and azotemia (102).

Copper data obtained in this study is in general agreement with published results. One exception is the data on copper in patients with diabetes mellitus. In the present study a direct relationship between the levels of glucose and copper was suggested in patients with diabetes mellitus.

Manganese levels were elevated in all diseases studied with exception of patients with leukemia and carcinoma of the prostate (under therapy).

**Table I**

**Serum Non-Dialyzable Copper and Manganese Levels in Various Diseases**

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>n</th>
<th>Micrograms per 100 ml</th>
<th>Copper</th>
<th>Manganese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>5</td>
<td>154.2 ± 45.5*</td>
<td>1.3 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis of the liver</td>
<td>5</td>
<td>229.9 ± 160.8</td>
<td>2.0 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Carcinoma of the prostate</td>
<td>7</td>
<td>389.5 ± 48.8</td>
<td>1.1 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>8</td>
<td>165.4 ± 36.5</td>
<td>1.9 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>14</td>
<td>164.1 ± 25.8</td>
<td>1.7 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>37</td>
<td>185.6 ± 59.2</td>
<td>2.0 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>58</td>
<td>145.0 ± 43.6</td>
<td>1.8 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Azotemia</td>
<td>102</td>
<td>160.2 ± 42.3</td>
<td>1.6 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>41</td>
<td>157.3 ± 38.2</td>
<td>1.3 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

*Standard deviation.

†Average leukocyte count was 110,700 cells/mm³; range 37,000-225,000.

‡Average acid phosphatase level was 3.8 Bodansky Units (B.U.); range 1.6-8.8.

§Extracted from previous publication (8) and additional data.

**Table II**

**Serum Non-Dialyzable Copper and Manganese Levels in Patients With Diabetes Mellitus**

<table>
<thead>
<tr>
<th>n</th>
<th>mgs/100 ml Glucose†</th>
<th>Micrograms per 100 ml Copper</th>
<th>Micrograms per 100 ml Manganese</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>172 (152–200)</td>
<td>134 (75–200)</td>
<td>2.0 (0.6–4.5)</td>
</tr>
<tr>
<td>17</td>
<td>234 (210–250)</td>
<td>142 (73–259)</td>
<td>1.6 (0.5–2.8)</td>
</tr>
<tr>
<td>15</td>
<td>282 (254–300)</td>
<td>140 (93–227)</td>
<td>1.6 (1.1–2.6)</td>
</tr>
<tr>
<td>6</td>
<td>343 (308–376)</td>
<td>150 (109–235)</td>
<td>1.8 (1.5–2.2)</td>
</tr>
<tr>
<td>9</td>
<td>482 (408–650)</td>
<td>177 (105–277)</td>
<td>1.9 (0.9–2.7)</td>
</tr>
</tbody>
</table>

†Normal glucose range: 70-110 mgs per 100 ml of serum.
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Table III

SERUM NON-DIALYZABLE COPPER AND MANGANESE LEVELS IN PATIENTS WITH AZOTEMIA

<table>
<thead>
<tr>
<th>n</th>
<th>mgs/100 ml Urea Nitrogen</th>
<th>Micrograms per 100 ml</th>
<th>Copper</th>
<th>Manganese</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>37 (30–48)</td>
<td>167 (93–280)</td>
<td>1.7 (0.7–3.6)</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>73 (52–100)</td>
<td>154 (79–224)</td>
<td>1.5 (0.7–2.6)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>150 (103–200)</td>
<td>166 (88–244)</td>
<td>1.8 (0.8–3.8)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>246 (202–290)</td>
<td>156 (120–190)</td>
<td>1.5 (0.8–2.1)</td>
<td></td>
</tr>
</tbody>
</table>

1Normal range: 7-18 mgs per 100 ml.

REFERENCES


