Trace Elements in Serum from Pakistani Patients with Acute and Chronic Ischemic Heart Disease and Hypertension

Shah Nawaz Khan,1 M. Ataur Rahman,1,3 and Abdus Samad2

We examined sera from 159 patients with ischemic heart disease and hypertension and from 50 apparently healthy control subjects for content of trace elements, cholesterol, triglyceride, and enzymes. Concentrations of copper, cobalt, cholesterol, and triglyceride were increased in all patients, but calcium was decreased in patients with hypertension, acute myocardial ischemia, and acute myocardial infarction. Also accompanying acute myocardial infarction were decreased concentrations of zinc and iron but increases in nickel, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. Magnesium concentration was lower in patients with acute myocardial ischemia. In acute myocardial infarction, the concentrations of copper, zinc, and iron were higher after 21–30 h (as compared with the values at 0–10 h), by which time concentrations of calcium, magnesium, cobalt, and alanine aminotransferase had decreased. The variation in concentration of trace elements in serum from cases of ischemic heart disease and hypertension corresponds to the severity of the disorder.

Additional Keyphrases: heart-related enzyme activity, myocardial infarction, cholesterol, triglyceride, electrolytes

Earlier workers have correlated vascular diseases with the hardness (mineral content) of drinking water (1, 2). Low concentrations of calcium in serum are associated with dysrhythmia and sudden death (3), whereas more magnesium in serum has been suggested to have a protective effect (4). On the other hand, Abraham et al. (5) reported that the concentration of magnesium was not associated with ischemic heart disease. Other trace elements that appear to be consistently related to malfunctioning of the cardiovascular system include sodium, copper (6), zinc (7), nickel (8), cobalt (7), and iron (9). Patterns of trace-element concentrations in tissues of subjects who died of atherosclerosis, hypertension, or myocardial infarction differ from those of healthy controls (10). The injured heart muscle shows decreased zinc concentration, which may be related to the loss of lactate dehydrogenase (LDH, EC 1.1.1.27) from infarcted heart tissue (7). The concentration of nickel decreases sharply in injured myocardium, then increases in plasma (11).

We have determined the concentrations of trace elements in serum from patients suffering from acute and chronic ischemic heart disease and hypertension, and we observed the variations of these values with time after an episode of acute myocardial infarction.

Materials and Methods

Subjects

Patients. Of 159 patients with different types of ischemic heart disease and hypertension, admitted or registered as outpatients at the National Institute of Cardiovascular Diseases, Karachi, 22 were classified as having angina pectoris, 28 with hypertension, 27 with acute myocardial ischemia, 56 with acute myocardial infarction, and 28 were patients who had had previous myocardial infarction. The diagnosis of angina pectoris was based on the patients' complaints of typical pain or pressure precipitated by exertion, emotion, or excitement, which was relieved by rest or sublingual nitroglycerin, and on results of their treadmill test.

The hypertensive patients had blood pressure exceeding 130/95 mmHg (systolic/diastolic); they were admitted for their uncontrolled hypertension and had previous histories of high blood pressure.

The patients with acute myocardial ischemia had a clinical history of chest pain, lasting for half an hour, which was relieved by rest; their electrocardiogram pattern indicated ischemia; and the activity of their heart-related enzymes was normal.

The patients with acute myocardial infarction showed two or more of the following criteria:

- Typical retrosternal pain or heaviness of recent onset and lasting more than 30 min.
- Electrocardiogram findings of pathological Q waves (0.045 duration, 4 mm depth or one fourth of the R wave) in leads not normally present (aVR and V1).
- Loss of progression of R wave in precordial leads. Q wave in lead 3 was taken as diagnostically significant for myocardial infarction in addition to the above. It was also associated with significant Q waves in leads 2 and aVF.
- Increased enzyme activity: Aspartate aminotransferase
(AST, EC 2.6.1.1) and LDH at 1.5-fold the upper limit of normal or greater.

Most of the patients with acute myocardial infarction had inferior-wall involvement. They were divided into five groups with respect to the time interval between the onset of chest pain and blood collection. The 0–10 h group consisted of 19 patients, the 11–20 h group of 15, the 21–30 h group of eight, the 31–50 h group of six, and the 72–h group of eight patients. The patients in the 31–50 h group for cobalt and nickel determination were only one in each case.

The "previous myocardial infarction" group consisted of patients who were asymptomatic now but who had been hospitalized at least three months previously with proven acute myocardial infarction. Their electrocardiogram pattern revealed old infarction.

All patients were in good health except for their cardiac condition and were in adequate nutritional status. They were well nourished and well developed.

Control subjects: Fifty apparently healthy subjects (44 men and six women, age 30–56 years) with no history of cardiovascular disease were selected to match the socioeconomic status of the patients. They were symptom free and their blood pressure and electrocardiogram patterns were normal. We noted their smoking habits and any family history of ischemic heart disease.

Procedures

Blood was sampled into plastic disposable syringes from patients and control subjects and collected in acid-aged (kept in 8 mol/L nitric acid for 24 h) glass tubes provided with plastic caps between 1000 and 1100 hours on the day of admission. Serum was separated from each sample within 2 h of its collection and stored at −10 °C until analyzed. No blood sample was drawn from the patients and control subjects within 3 h of eating.

We determined copper and zinc in serum (12), iron (13), nickel as complexed with ammonium pyrrolidine diithiocarbamate (14), and cobalt complexed with 1-pyrrolidine carbodithionate (15) with an atomic absorption spectrophotometer (Model 403; Perkin-Elmer Corp., Norwalk, CT). Serum calcium was determined by titration with EDTA (16) and serum magnesium with the kit supplied by Heinz Haury Chemische Fabrik, Munchen, F.R.G., with Titan Yellow as color reagent. Serum sodium and potassium were determined by flame photometry. AST and alanine aminotransferase (ALT, EC 2.6.1.2) were assayed with use of kits

<table>
<thead>
<tr>
<th>Table 1. Concentrations of Some Analytes in Serum from Control Subjects and Patients with Ischemic Heart Disease and Hypertension</th>
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</thead>
<tbody>
<tr>
<td>Copper, µg/L</td>
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<tr>
<td>Zinc, µg/L</td>
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<tr>
<td>Iron, µg/L</td>
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<tr>
<td>Nickel, µg/L</td>
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<tr>
<td>Cobalt, µg/L</td>
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<td>Sodium, mmol/L</td>
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<td>Potassium, mmol/L</td>
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<tr>
<td>Calcium, mg/L</td>
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<tr>
<td>Magnesium, mg/L</td>
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<tr>
<td>AST, U/L</td>
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<td>ALT, U/L</td>
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<td>LDH, U/L</td>
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<tr>
<td>Cholesterol, mg/L</td>
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<tr>
<td>Triglyceride, mg/L</td>
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</tbody>
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Values are expressed as mean ± SEM. No. of observations given in parentheses.
Differences statistically significant as compared with control: *p < 0.001, **p < 0.01, ***p < 0.02, ****p < 0.05.
supplied by Sigma Chemical Co., St. Louis, MO (kit no. 505). LDH was determined with a kit supplied by Dade Diagnostics Inc., Miami, FL. Serum triglycerides were determined with a kit from Sigma Chemical Co. (kit no. 405) and cholesterol by the method of Watson (17), with ammonium 2,5-dimethylbenzosulfonate as color reagent.

### Table 2. Age, Sex, and Risk Factors for Patients with Ischemic Heart Disease and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Angina pectoris</th>
<th>Hypertension</th>
<th>Acute myocardial infarction</th>
<th>Acute myocardial infarction</th>
<th>Old myocardial infarction</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
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<tr>
<td>No. of subjects</td>
<td>Total Men</td>
<td>Tobacco smokers</td>
<td>Positive family history</td>
<td>Blood pressure, mean ± SEM, mmHg</td>
<td>Blood pressure, mean ± SEM, mmHg</td>
<td>Blood pressure, mean ± SEM, mmHg</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>42</td>
<td>27</td>
<td>12</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Men</td>
<td>27</td>
<td>12</td>
<td></td>
<td>119.5 ± 1.3</td>
<td>132.1 ± 2.7</td>
<td>130.5 ± 2.2</td>
</tr>
<tr>
<td>Women</td>
<td>23</td>
<td>8</td>
<td></td>
<td>77.3 ± 0.8</td>
<td>85.2 ± 1.2</td>
<td>83.8 ± 2.5</td>
</tr>
<tr>
<td>Blood pressure, mean ± SEM, mmHg</td>
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<tr>
<td>Systolic</td>
<td>119.5 ± 1.3</td>
<td>132.1 ± 2.7</td>
<td>130.5 ± 2.2</td>
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<tr>
<td>Diastolic</td>
<td>77.3 ± 0.8</td>
<td>85.2 ± 1.2</td>
<td>83.8 ± 2.5</td>
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*Mean ± SEM (and range).

**Significantly different from control group.

**Results**

In angina pectoris only the copper concentration was increased, whereas in hypertension copper, cobalt, sodium, cholesterol, and triglycerides were all increased and calcium was decreased as compared with control subjects (Table 1). In patients with acute myocardial ischemia, copper, cobalt, cholesterol, and triglycerides increased and calcium and magnesium decreased (Table 1). The patients with acute myocardial infarction showed the most dramatic changes in trace element concentrations. Copper, nickel, cobalt, ALT, AST, LDH, cholesterol, and triglycerides increased; zinc, iron, and calcium decreased. In patients with old myocardial infarction, copper, sodium, ALT, LDH, cholesterol, and triglycerides increased (Table 1).

Table 2 compares age, sex, and various risk factors for patients with ischemic heart disease with the same factors in control subjects. Many more men than women were affected. Of all the patients studied, 62.3% were smokers. The blood pressure was increased in all groups except the patients with acute myocardial infarction. Only 27% of the patients had a previous family history of heart disease.

Figure 1 shows the changes in serum analytes from patients with acute myocardial infarction vs. time lapsed after the chest pain. Copper and zinc increased with time, whereas iron, sodium, and potassium increased for about 21–30 h after an acute myocardial infarction, then returned to normal values. Nickel, cobalt, calcium, and magnesium decreased until 21–30 h after the chest pain episode. Although the enzyme activities initially decreased, they returned to 0–10 h values. The cholesterol concentration increased between 31 and 72 h after the infarct, whereas triglycerides decreased slightly.

**Discussion**

All the categories of patients investigated showed a significant increase in their concentrations of serum copper (Table 1), which exceeded the value for plasma we reported earlier (18). This increase is probably explained by increase of serum copper concentrations with age (19), the age of the group in the earlier report being 16–30 years, while in the present study the ages of control subjects range from 30 to 56 years. In angina pectoris, copper was the only analyte we
investigated that was increased in serum. In hypertensive patients, besides copper, the cobalt, cholesterol, and triglyceride concentrations also increased. Again, these patients averaged 10 years older than the control subjects, and cholesterol and copper increase with age, so this may not be exclusively ascribed to the disease. The association of trace elements with other nonacute cardiac conditions, such as angina pectoris and hypertension, is not well established, except for the increase in serum copper, which remains high in all ischemic heart disease patients. Serum contains higher concentrations of copper, zinc, and iron than plasma, a difference that may be as much as 50 to 150 μg/L. Hall (20) observed that the concentration of iron in serum shows a diurnal variation, reaching maximum values by 0900 hours (approximately the time at which the specimens were collected in the present study).

The acute cardiac conditions showed a wide variation of trace-element concentrations in sera. The reports of Khandker et al. (21), Versieck et al. (22), and Masironi (23) confirm our findings of high values for serum copper, while Versieck et al. (22) also reported higher values of serum nickel and Wester (24, 25) reported increases in cobalt. Decreased concentrations of serum zinc and iron have been confirmed by Handjani et al. (26) and Versieck et al. (22), respectively. The further increase in serum copper with time after the infarct episode (Figure 1) may be due to damage of the heart tissue. After the initial increase, serum nickel and cobalt did not increase further and the decrease in iron did not vary significantly with increased time after the attack. The lower concentrations of serum zinc were relatively higher 72 h after the episode (Figure 1). This may indicate that the initial changes in the trace elements are a secondary effect of acute myocardial infarction.

Calcium and magnesium are involved in the enzyme system of the myocardium and in maintaining electrolyte balance. Serum calcium decreased in acute myocardial ischemia and infarction, while serum magnesium decreased only in acute myocardial ischemia (Table 1); these values varied somewhat with time in acute myocardial infarction (Figure 1). Berberian (27) and Bloch (28) have suggested that magnesium depletion is a significant etiological factor in the development of ischemic heart disease, but Abraham et al. (5) found no significant association between serum magnesium and ischemic heart disease. Low concentrations of serum calcium have also been related to heart arrhythmias, which are often observed in patients with ischemic heart disease (3).

We found serum cholesterol and triglycerides to be increased significantly in all the ischemic and hypertensive patients as compared with the control group (Table 1). Most of our patients have serum cholesterol concentrations below the normal range published for U.S.A. and European populations but higher than the values for control subjects. In an earlier report (29), the upper limit for serum cholesterol was considered to be 1800 mg/L in Pakistan. The hypercholesterolemia in patients with ischemic heart disease is unlikely to be secondary to the trace element imbalance in the body.

Smoking was the most important risk factor noted, 62.3% of all the patients being either current or former smokers (Table 2). Some evidence indicates that the influence of smoking is independent of, but also synergistic with, other risk factors such as hypertension and high blood concentration of cholesterol (30). Only 27% of the patients had a positive family history of ischemic heart disease, as compared with 24% in the control group, which indicates no causal relationship of this factor with the disease. A significant increase in the blood pressure in patients of all categories except those with acute myocardial infarction was observed (Table 2).

Possibly some of the observed changes in trace-element concentrations may be related to dietary sources, as regional differences have been demonstrated reflecting the dietary intake. For example, differences in serum zinc in the U.S.A. have been related to the regional differences in dietary zinc intakes. Although a cause-and-effect relationship between a certain trace element and a given cardiovascular syndrome is not established, changes in trace elements concentrations may play an important biochemical role in ischemic heart disease.

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References


