Magnesium and Trace Metals: Risk Factors for Coronary Heart Disease?

Associations Between Blood Levels and Angiographic Findings

JOACHIM MANTHEY, M.D., MARKUS STOEPPLER, PH.D., WOLFGANG MORGENSTERN, EGBERT NÖSSEL, M.D., DIETER OPHERK, M.D., ANDREA WEINTRAUT, M.D., HORST WESCH, PH.D., AND WOLFGANG KÜBLER, M.D.

SUMMARY A deficiency or an excessive intake of metals with cardiovascular effects is suspected to be involved in the pathogenesis of coronary heart disease (CHD) and sudden death. Therefore, in 106 patients undergoing coronary arteriography, serum levels of six essential metals (magnesium, chromium, copper, manganese, selenium, and zinc) and whole blood concentrations of two elements without known essential function (cadmium and lead) were measured using atomic absorption spectrophotometry, including the flameless technique, or neutron activation analysis.

The patients were classified into three groups according to severity of CHD as assessed by coronary angiography: those without coronary lesions (n = 31) and those with moderate (n = 34) or severe CHD (n = 41). Patients with severe CHD had lower mean serum magnesium and higher serum copper and manganese levels than those without CHD (magnesium, 1.63 ± 0.16 [SD] vs 1.78 ± 0.16 mg/dl, p < 0.005; copper, 1.39 ± 0.22 vs 1.24 ± 0.24 mg/dl, p < 0.05; manganese, 1.30 ± 0.43 vs 1.05 ± 0.40 μg/dl, p < 0.05). In contrast, metal concentrations in patients with moderate CHD did not differ significantly from control values. There was no significant association between prevalence and severity of CHD and the other elements investigated. Analysis of associations between metal concentrations and clinical characteristics revealed markedly elevated blood cadmium levels in cigarette smokers compared with nonsmokers (2.49 ± 1.72 [n = 28] vs 0.43 ± 0.22 μg/dl [n = 18], p < 0.001). A correlation was noted between cadmium levels and the number of cigarettes smoked per day (r = 0.725, p < 0.001).

Our results suggest that a deficiency of magnesium but not of the other metals studied may be present in patients with severe CHD; elevated serum copper and manganese levels do not play a role in the development of CHD in the sample of patients studied; and cigarette smoking may be associated with increased serum cadmium levels, which may explain in part the contribution of smoking to the risk of sudden death in patients with CHD.

THE SIGNIFICANCE of elevated serum cholesterol levels, arterial hypertension, and cigarette smoking as risk factors for the development of coronary heart disease (CHD) has been well documented in numerous studies. An epidemiologic study by Keys et al. indicated that variables other than traditional risk factors may contribute to the risk of CHD among American men. Furthermore, there are regional differences in the death rate caused by CHD that are not fully understood. In the search for other causes of CHD, attention is being focused on metal and trace element imbalance.

Deficiency states of several essential metals owing to low dietary intake or failure of homeostatic control mechanisms have been suggested as causes of CHD and/or sudden death. It has also been assumed that an excessive intake of various elements such as copper and cadmium may contribute to regional differences in cardiovascular mortality. However,
only a few studies relate metals and trace elements as determined in human blood samples to CHD. These investigations have yielded conflicting results because the diagnosis of CHD has been established only by clinical data but not by angiographic findings. To evaluate the significance of a relationship between metals and CHD, one must determine if there is a true independent association between metals and CHD. Therefore, we have attempted to relate serum or whole blood levels of metals to the extent of CHD in patients undergoing coronary angiography. We also compared metal concentrations with traditional risk factors and other clinical characteristics related to CHD.

Methods

Patients

This study involved 106 consecutive patients referred to the Department of Cardiology at the University of Heidelberg for evaluation of chest pain. Only male subjects were studied to avoid confusions by potential sex differences in metal concentrations reported for copper and zinc. Patients with congenital or valvular heart disease, cardiomyopathy and overt pulmonary disease were excluded.

Clinical and Laboratory Procedures

Clinical data were collected on the day after admission and before coronary arteriography. Blood pressure was measured after at least 30 minutes of bed rest with a standard cuff sphygmomanometer. Fasting serum cholesterol and triglyceride levels and plasma sodium, potassium, and calcium concentrations were measured using standard laboratory procedures. Blood samples were drawn by venous puncture without tourniquet using Teflon catheters (Quick-Kath, Travonel Laboratories, Inc.) after an overnight fast. To prevent blood coagulation, sodium EDTA (1 mg/ml) was added.

Recently developed techniques based on flameless atomic absorption spectrophotometry were used to determine chromium, manganese, copper, cadmium and lead levels. The analytical system consisted of a Perkin-Elmer Model 300 S or 400 atomic absorption spectrophotometer equipped with a Perkin Elmer model 56 recorder, a deuterium background corrector and an HGA 72 or 74 graphite tube atomizer. Measurements of magnesium and zinc were performed by an atomic absorption flame technique. Selenium was determined by neutron activation analysis as described previously. The accuracy of these methods has been confirmed by concurrent measurements using a second independent technique, including the low-temperature ashing procedure and the direct analysis (chromium), the neutron activation analysis vs the atomic absorption spectrophotometry (copper, magnesium, selenium and zinc), and the differential pulse anodic stripping voltammetry vs the flameless atomic absorption spectrophotometry (cadmium and lead). Analysis of Reference Material 1577 yielded results corresponding to 103% (magnesium), 99% (copper), 96% (manganese), 101% (selenium), 95% (zinc), 93% (cadmium) and 94% (lead) of the mean values given by the National Bureau of Standards. The day-to-day precision, expressed by the variation coefficients obtained from 15 consecutive measurements was <15% (cadmium and manganese), <10% (chromium, lead, selenium), <5% (copper, zinc), and <1% (magnesium).

Arterial and left-heart pressures were measured using a Statham P23Db pressure transducer before injecting contrast material. Single-plane 35-mm cineangiograms of the left ventricle were filmed at 50 frames/sec in the 30° right anterior oblique position after injection of 40–50 ml of Urografin 76 into the left ventricle. Left ventricular ejection fraction was calculated using the area-length method. Selective coronary arteriography was performed either with the Sones or with the Judkins technique. For visualization of the right coronary artery, at least three projections were used and for the left coronary artery at least six projections, including hemi-axial views, were used. The angiograms were interpreted independently by two experienced cardiologists. Estimates of the severity of coronary lesions by two observers were highly correlated (r = 0.89, n = 50). If their estimation of coronary artery lesions differed, a third observer reviewed the film. Coronary angiograms were classified as normal if the left main, circumflex, left anterior descending, and right coronary arteries each contained less than 25% stenosis. Patients who had 25% or greater stenosis of one or more of the coronary arteries were classified as having CHD. To quantify the extent and severity of the coronary lesions, Gensini's severity score was used. A score of less than 32 units indicated moderate CHD and a score of 32 units or greater indicated severe CHD.

Statistical Methods

The data were analyzed using the chi-square approach for categorical data and analysis of variance followed by Scheffe's test for comparison between multiple groups. The statistical software package developed by Nie et al. was used.

Results

Clinical Profile

Thirty-one of the 106 patients investigated had no detectable CHD, congenital or valvular heart disease, cardiomyopathy or overt pulmonary disease. Most patients had atypical angina and none had suffered a previous myocardial infarction. These patients therefore served as normal controls (group 1). The remaining 75 patients had 25% or greater stenosis of one or more of the major coronary arteries. Thirty-four were classified as having moderate CHD (group 2) and 41 as having severe CHD (group 3). Clinical characteristics for each group are listed in table 1. The mean age differed significantly (p < 0.001) between control subjects (43 years) and patients with CHD (group 2,
mean age 49 years and group 3, 50 years). Forty-seven percent of group 2 patients and 73% of group 3 patients had a history of myocardial infarction. Patients using digitalis and diuretics were usually in groups 2 and 3. Cholesterol levels were significantly higher \((p < 0.05)\) in patients with than without CHD. Similarly, concentrations of serum triglycerides tended to be higher in patients with CHD (group 2, 235 ± 132 mg/dl and group 3, 274 ± 154 mg/dl) than in controls (191 ± 117 mg/dl) (NS). Neither ejection fraction nor left ventricular end-diastolic pressure (LVEDP) differed significantly between group 1 and group 2; but group 3 patients showed a depressed ejection fraction and an elevated LVEDP compared with group 2 and group 1 patients. Proportionately more patients with a history of cigarette smoking were in the groups with CHD (79% of group 2 and 89% of group 3) than in controls (71%), but the differences were not significant \((p > 0.05)\). There were no significant differences among the groups with respect to systolic and diastolic blood pressure.

**Relation of Metal Concentrations to the Extent of CHD**

Table 2 is a list of the blood metal concentrations in the three groups. Only magnesium, copper and manganese levels were significantly different between the groups. Serum magnesium levels were lower in patients with CHD compared with control subjects (fig. 1), but serum copper (fig. 2) and manganese (fig. 3) were higher in CHD patients than in controls. However these differences were not significantly different only if control subjects (group 1) and patients with severe CHD (group 3) were compared \((p < 0.05)\). Furthermore, the significant differences were for group means and there was no serum level of any metal that would distinguish individual patients from patients in other groups. No significant associations could be demonstrated for CHD and the other metals investigated, including sodium, potassium and calcium.

**Relation of Metal Concentrations to Clinical Characteristics**

We found some clinical characteristics to be related to metal concentrations. Patients who were taking digitalis had lower serum magnesium levels than patients who were not on digitalis therapy \((1.67 ± 0.16 \text{ mEq/L} [n = 63] \text{ vs } 1.76 ± 0.15 \text{ mEq/L} [n = 38], p < 0.02)\). Patients who were using diuretics had lower serum magnesium than those who did not \((1.62 ± 0.11 \text{ mEq/L} [n = 13] \text{ vs } 1.72 ± 0.16 \text{ mEq/L} [n = 88], p < 0.05)\). There was no association between

### Table 1. Clinical Characteristics of Patients Grouped According to Severity of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (control) n = 31</th>
<th>Group 2 (mod. CHD) n = 34</th>
<th>Group 3 (sev. CHD) n = 41</th>
<th>p (group 3 vs 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>43 ± 8</td>
<td>49 ± 6</td>
<td>50 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>History of MI†</td>
<td>0</td>
<td>47% (16)§</td>
<td>73% (30)§</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Use of digitalis†</td>
<td>32% (10)</td>
<td>68% (23)$§</td>
<td>73% (30)$§</td>
<td>NS</td>
</tr>
<tr>
<td>Use of diuretics†</td>
<td>3% (1)</td>
<td>9% (3)</td>
<td>22% (9)§</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)*</td>
<td>214 ± 32</td>
<td>251 ± 48§$</td>
<td>246 ± 61§</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (%)*</td>
<td>72 ± 7</td>
<td>65 ± 4</td>
<td>55 ± 14§</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDP (mm Hg)*</td>
<td>7 ± 2</td>
<td>9 ± 4</td>
<td>13 ± 8§</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.
†Values in parentheses indicate number of patients.
§p < 0.001 vs group 1.
¶p < 0.001 vs group 1.

Abbreviations: MI = myocardial infarction; LVEDP = left ventricular end-diastolic pressure.

### Table 2. Comparison of Metal Concentrations in Patients Grouped According to Severity of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Metal</th>
<th>Group 1 (control)</th>
<th>Group 2 (mod. CHD)</th>
<th>Group 3 (sev. CHD)</th>
<th>p (group 3 vs 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium (serum, mEq/l)</td>
<td>1.78 ± 0.16 (31)</td>
<td>1.72 ± 0.15 (31)</td>
<td>1.63 ± 0.16 (39)†</td>
<td>NS</td>
</tr>
<tr>
<td>Chromium (serum, µg/l)</td>
<td>0.42 ± 0.24 (31)</td>
<td>0.41 ± 0.16 (34)</td>
<td>0.40 ± 0.15 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Copper (serum, mg/l)</td>
<td>1.24 ± 0.24 (31)</td>
<td>1.31 ± 0.25 (34)</td>
<td>1.39 ± 0.22 (40)§</td>
<td>NS</td>
</tr>
<tr>
<td>Manganese (serum, µg/l)</td>
<td>1.05 ± 0.40 (31)</td>
<td>1.19 ± 0.41 (34)</td>
<td>1.30 ± 0.43 (39)§</td>
<td>NS</td>
</tr>
<tr>
<td>Selenium (serum, µg/l)</td>
<td>101 ± 21 (24)</td>
<td>116 ± 25 (32)</td>
<td>106 ± 17 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>Zinc (serum, mg/l)</td>
<td>0.99 ± 0.20 (31)</td>
<td>1.04 ± 0.17 (34)</td>
<td>1.03 ± 0.15 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Cadmium (whole blood, µg/l)</td>
<td>1.35 ± 1.68 (25)</td>
<td>1.29 ± 1.38 (27)</td>
<td>1.27 ± 1.14 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Lead (whole blood, µg/l)</td>
<td>164 ± 48 (30)</td>
<td>149 ± 56 (29)</td>
<td>150 ± 60 (38)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
Numbers in parentheses refer to number of patients.
*\(p < 0.05\).
†\(p < 0.005\).
the use of digitalis and diuretics and serum levels of the other metals studied. Furthermore, we observed a highly significant correlation between serum magnesium and left ventricular ejection fraction (r = 0.3881, p < 0.001) and a poor inverse correlation between serum magnesium and LVEDP (r = –0.2004, p < 0.05). Cholesterol was related to serum copper (r = 0.2064, p < 0.05) and to serum manganese (r = 0.2300, p < 0.05). Another positive correlation was noted between serum manganese and both systolic (r = 0.3356, p < 0.001) and diastolic blood pressure (r = 0.3882, p < 0.001). No association was found between the other metals studied and age, serum lipids, ejection fraction, LVEDP and blood pressure.

Copper, cadmium and lead bore a significant association to smoking habits. The major differences between smokers, exsmokers and nonsmokers were noted in the cadmium levels, which averaged 2.49 ± 1.72 μg/l (n = 28) in smokers, 0.81 ± 0.60 μg/l (n = 36, p < 0.001). In exsmokers and 0.43 ± 0.22 μg/l (n = 18, p < 0.001) in nonsmokers. Exsmokers who had abstained from smoking more than 6 and less than 12 months showed lower cadmium levels than current smokers (p < 0.001) but higher cadmium levels than patients who had never smoked (p < 0.001). Cadmium levels of exsmokers who stopped smoking for more than 12 months were within normal limits (fig. 4). There was a significant correlation between the cadmium levels and the number of cigarettes smoked per day (fig. 5) (p < 0.001). Less marked differences between smokers, exsmokers and nonsmokers were found in copper and lead concentrations. Cigarette smokers had serum copper levels 13% higher (1.37 ± 0.26 mg/l [n = 28] vs 1.21 ± 0.21 mg/l [n = 21], p < 0.05) and blood lead levels which were 24% higher (164 ± 49 μg/l [n = 27]) vs 132 ± 32 μg/l [n = 22], p < 0.05) than those of nonsmokers. Serum copper and blood lead levels of exsmokers (copper, 1.34 ± 0.21 mg/l [n = 55]; lead, 143 ± 48 μg/l [n = 48]) did not differ significantly from those of both smokers and nonsmokers.

**Discussion**

This is the first systematic investigation of relations between blood metal levels and the severity of CHD as evaluated by selective coronary arteriography. Blood metal concentrations were measured by newly developed methods, including flameless atomic absorption spectrophotometry and neutron activation analysis.

**Validity of Methods**

During the past decade, methods for accurate and sensitive analysis of metals in human blood samples have been developed. Recent studies have revealed lower blood metal concentrations compared with some previous findings, either because of more careful prevention of contamination or because the more recent techniques are more specific. In particular,
values. The data presented in this paper agree well with the more recent data from flameless atomic absorption spectrophotometry or neutron activation analysis.

Significance of Magnesium Deficiency in CHD

One of the striking findings in this paper is that patients with severe CHD have significantly lower serum magnesium levels than patients without the disease. In previous investigations there were positive\textsuperscript{66} and negative findings\textsuperscript{97} with regard to a relationship between serum magnesium levels and CHD. However, the extent of CHD as estimated by coronary angiography was not reported. Therefore, the different observations may be explained by different patient populations.

Interest in the role of magnesium in CHD has been stimulated markedly by experimental, epidemiologic and clinical findings, suggesting that a magnesium deficiency may be implicated in the pathogenesis of hypercholesterolemia and sudden death in patients with CHD.\textsuperscript{15, 16, 84, 99} There has not been agreement, however, that a magnesium deficiency is necessarily correlated with hypercholesterolemia in patients with CHD.\textsuperscript{90} We could not demonstrate any significant association between serum magnesium and lipid levels, suggesting that a magnesium deficiency seems to be of little importance for the development of hyperlipidemia and arterial lesions leading to CHD.

It is well known that hypomagnesemia can contribute to disturbances in cardiac rhythm, especially when associated with digitalis administration.\textsuperscript{90} Therefore, the finding of depressed serum magnesium levels in patients with severe CHD (and consequently with a high risk of serious cardiac rhythm disturbances) is of
particular clinical significance and may be an additional explanation for the risk of sudden death in these patients.

Depressed serum magnesium levels were observed only in group 3 patients with severe CHD and left ventricular dysfunction. Left ventricular function as assessed by ejection fraction showed a highly significant correlation with serum magnesium levels. Therefore, one may speculate that impaired left ventricular function is responsible for the depressed serum magnesium levels in patients with severe CHD rather than inadequate dietary intake, as suggested in epidemiologic studies. Whether the low serum magnesium levels in these patients are the consequence of humoral compensatory mechanisms in heart failure (such as stimulation of the renin-angiotensin system or of the sympathetic nervous system) or are the consequence of digitalis or diuretic therapy cannot be definitely answered.

**Essential Trace Metals and CHD**

Of the trace metals investigated in this study, only copper and manganese were found to be associated with CHD. Our findings confirm previous studies reporting elevated serum copper and manganese levels in patients with angina pectoris or with previous myocardial infarction. On the other hand, we could not find a significant association between chromium, selenium and zinc and CHD. Our findings are in contrast to studies in which depressed serum zinc and chromium levels in patients with CHD were observed. Differences in the analytical methods may account for these different observations.

Our data do not support the concept that trace elements are independent risk factors for CHD. Elevated levels of serum copper and manganese were found only in patients with severe CHD but not in patients with moderate CHD, suggesting that these differences are not related to the pathogenesis of CHD but are more related to differences between the patients with moderate and with severe CHD. The mechanisms underlying the associations between severe CHD and elevated serum copper and manganese levels, however, must be clarified.

**Possible Role of Cadmium in CHD**

The possibility that cadmium produces cardiovascular diseases, especially arterial hypertension, has been suggested. In this study we showed that blood cadmium levels in humans are predominantly determined by smoking habits. Cadmium levels were markedly higher in smokers compared with nonsmokers; a highly significant correlation was observed between cadmium levels and the number of cigarettes smoked per day. Zielhuis et al. reported blood cadmium levels in excellent agreement with our data. They also found significantly elevated cadmium levels in smokers; however, the difference between smokers and nonsmokers was less marked than in our study. This difference may be explained by the higher proportion of heavy smokers among our patients. No data are available in previous reports relating cadmium blood levels and the time passed after quitting cigarette smoking.

The effects of cadmium on the development of arterial hypertension are controversial. Glauser et al. found that hypertensive patients had higher blood cadmium levels than normotensive subjects. However, they did not report smoking habits in that investigation. In our study, there was no correlation between cadmium levels and blood pressure. This observation is consistent with that of Beevers et al. Therefore, cigarette smoking, which has been recognized as a source of exposure to cadmium, does not appear to be implicated as a major factor in the genesis of elevated blood pressure in humans.

Recently, long-term exposure to small doses of cadmium was found to decrease the content of high-energy phosphate in rat hearts. In liver mitochondria, cadmium has been found to cause un-
coupling of oxidative phosphorylation. Such effects of cadmium on the cellular level may be an additional mechanism responsible for the higher incidence of sudden death in smokers compared with nonsmokers. The normal cadmium levels in exsmokers who stopped smoking for more than 1 year may explain in part that cessation of cigarette smoking is associated with reduced mortality among patients with CHD.

Implications

This study suggests that patients with severe but not with moderate CHD have lower serum magnesium and higher serum copper and manganese levels than subjects with normal coronary arteries. These associations of metals with severity of coronary artery lesions appear to be secondary to associations with other variables. The finding of low serum magnesium levels among patients with severe CHD, and consequently with a high risk of sudden death, supports the theory that a magnesium deficiency may contribute to the development of serious cardiac rhythm disturbances in these patients. However, our results do not support the hypothesis that a deficiency of the elements investigated may be important risk factors for the development of CHD. The presence of highly elevated cadmium levels in heavy cigarette smokers may be an additional explanation for the powerful contribution of cigarette smoking to the risk of sudden death in patients with CHD. Finally, the determination of cadmium levels allows objective assessment of smoking habits and may be an excellent tool for monitoring smoking habits in epidemiologic studies.

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Magnesium and trace metals: risk factors for coronary heart disease? Association between blood levels and angiographic findings.
J Manthey, M Stoeppler, W Morgenstern, E Nüssel, D Opherk, A Weintraut, H Wesch and W Kübler

Circulation. 1981;64:722-729
doi: 10.1161/01.CIR.64.4.722

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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