

Plasma zinc in acute myocardial infarction

Diagnostic and prognostic implications

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Zinc is a metal component of many important enzymes, and its availability controls the rate of synthesis of nucleic acids and protein. Serum zinc levels have been shown to fall after acute tissue injury, including myocardial infarction.

The purpose of this clinical study was to examine the value of serial plasma zinc measurements in a coronary care unit. Studies were made on 188 patients: 88 with unequivocal myocardial infarction, 52 controls, and 48 in a borderline group.

Patients with myocardial infarction showed a fall in plasma zinc within the first three days, whereas patients in the other two groups did not. The difference in the mean minimum zinc levels between the groups with and without infarction was highly significant.

In patients with myocardial infarction there was good correlation between the minimum plasma zinc level and the peak value of plasma enzymes, and also with some clinical estimators of prognosis. A fall in plasma zinc is a reliable diagnostic test for acute myocardial infarction, and the extent of the fall has prognostic implications.

Zinc is the metal component of many important enzymes, including carbonic anhydrase, alkaline phosphatase, various proteases, and many dehydrogenases (Wacker, Ulmer, and Vallee, 1956; Li, 1966; Orten, 1966). The availability of zinc governs the tissue concentrations and activity of zinc metallo-enzymes, and also the rate of synthesis of nucleic acids and protein.

Serum zinc levels have been shown to fall after acute tissue injury (Halsted and Smith, 1970), including myocardial infarction (Wacker *et al.*, 1956; Halsted and Smith, 1970; Lindeman *et al.*, 1973; Handjani *et al.*, 1974). In myocardial infarction the levels fall within one or two days of the onset, and then rise to reach normal levels in 10 to 14 days. The clinical studies reported so far (Wacker *et al.*, 1956; Handjani *et al.*, 1974) have investigated relatively small numbers of patients, and there has been little attempt to correlate the zinc levels with other biochemical measurements, or with prognosis. Thus, it is not yet established whether measurement of plasma zinc has any practical value in myocardial infarction.

The purpose of this study was to examine within

the context of a coronary care unit the value of serial plasma zinc measurements. The first objective was to evaluate the usefulness of this test in distinguishing patients with acute myocardial infarction from those with chest pain not due to infarction. The second was to study the relation between plasma zinc and other biochemical and clinical prognostic indices usually measured in myocardial infarction.

Subjects and methods

Methods

The 206 patients admitted to the Coronary Care Unit of the Princess Margaret Hospital between August 1974 and January 1975 were the subject of this study.

Blood was collected for investigations on the first, second, third, and tenth day without regard to the fasting state. It was collected in plastic syringes, avoiding haemolysis and contamination by metals.

Creatine kinase (CK) was measured by a kinetic method using the Vitatron¹ apparatus. Serum aspartate aminotransferase (AST), lactic dehydrogenase (LDH), and hydroxybutyric dehydrogenase

¹Made by Vitatron, Holland.

(HBD) were measured by the colorimetric method, using kits. Plasma zinc was measured by atomic absorption spectrophotometry, after precipitating plasma protein with trichloroacetic acid (Hackley *et al.*, 1968).

Statistical analysis of the data was performed on the University of Canterbury Burroughs Computer, using standard programmes.

Patient groups

Patients were included in this study if at least two measurements of plasma enzymes and zinc were obtained between the first and third days after admission. Adequate data were obtained in 188 patients out of 206 consecutive admissions. These 188 patients were divided into three groups as shown in Table 1.

TABLE 1 *Patient groups*

1	Acute myocardial infarction	88
	1A—Without cardiac arrest or death	70
	1B—With cardiac arrest and/or death	18
2	Control group	52
3	Intermediate group	48

Group 1 consisted of 88 patients with unequivocal myocardial infarction. This group was further subdivided into group 1A comprising 70 patients without major arrhythmic complications (ventricular fibrillation or asystole) or mortality, and group 1B comprising 18 patients who suffered reversible cardiac arrest or who died. The diagnosis of myocardial infarction was based on a characteristic history, sequential electrocardiographic abnormalities, and a diagnostic rise in plasma enzymes.

Group 2, consisting of 52 patients, was the control group. All these patients had normal serial enzymes and electrocardiograms recorded daily for 3 days. No evidence of cardiac muscle injury emerged during the week-long period of hospital observation. Hence their chest pain was considered not to be the result of cardiac infarction. However, in the absence of coronary angiographic studies, cardiac ischaemia without infarction as a cause of the pain cannot be conclusively excluded.

Group 3 was an intermediate group of 48 patients who had an equivocal rise in plasma enzymes, and/or electrocardiograms which showed ischaemic changes. It is probable that a number of these patients suffered prolonged ischaemic pain without actual infarction.

Results

In those patients who had sustained cardiac infarction (group 1) the plasma zinc level fell within the

TABLE 2 *Mean daily plasma zinc levels ($\mu\text{g}/100\text{ ml}$)*

Group	Day 1		Day 2		Day 3		Day 10	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	92.53	17.66	79.32	13.87	76.83	17.09	96.32	9.45
2	96.95	16.67	97.43	17.14	95.71	17.31	100.11	9.60
3	88.25	11.22	90.28	12.15	90.03	12.07	96.92	11.00

Normal range=90–118 $\mu\text{g}/100\text{ ml}$.

Conversion from Traditional Units to SI units:

1 $\mu\text{g}/100\text{ ml} \approx 0.153\text{ }\mu\text{mol/l}$.

first three days after infarction (Table 2) and then rose to normal or near-normal levels by the tenth day. Patients in groups 2 and 3 did not show this fall.

Diagnostic implications

The usefulness of plasma zinc in diagnosis of myocardial infarction was ascertained by comparing the mean minimum plasma zinc levels in the three groups (Table 3). There was a highly significant difference between the mean minimum plasma zinc levels of group 1 and group 2, and also between group 1 and group 3. There was no significant difference between the mean minimum plasma zinc levels of groups 2 and 3. When group 1 was further subdivided into groups 1A and 1B the difference between these two subgroups was also highly significant.

TABLE 3 *Minimum plasma zinc levels*

Group	Number	Minimum plasma zinc ($\mu\text{g}/100\text{ ml}$)		
		Mean	Standard deviation	Standard error of mean
1	88	68.63	14.63	1.56
1A	70	72.07†	12.25	1.46
1B	18	55.22†	15.73	3.71
2	52	84.52*	12.26	1.70
3	48	84.60*	11.58	1.67

*Significant difference from Group 1 ($P < 0.001$)

†Significant difference between Groups 1A and 1B ($P < 0.001$)

Conversion from Traditional Units to SI units:

1 $\mu\text{g}/100\text{ ml} \approx 0.153\text{ }\mu\text{mol/l}$.

Correlation with plasma enzymes

The zinc results for patients with myocardial infarction (group 1) were compared with the results of other laboratory tests used in this context, namely the enzymes CK, AST, LDH, and HBD.

Statistical analyses were made with both the minimum plasma zinc level and the change in plasma zinc (the difference between the highest and

lowest measurement in each patient). The peak level of each of the enzymes was used, and when this was above the usually-measured range, the upper limit of the range was used for the purposes of analysis.

Each enzyme correlated significantly with both the minimum plasma zinc level and the change in plasma zinc, and most of these correlated at a highly significant level (Table 4).

TABLE 4 Correlation between plasma zinc and plasma enzymes

	Group 1 (n=88)			
	Minimum zinc r	P	Change in zinc r	P
CK	-0.36	0.001	0.42	0.001
AST	-0.22	0.05	0.34	0.001
LDH	-0.34	0.001	0.49	0.001
HBD	-0.22	0.05	0.38	0.001

Prognostic implications

In order to determine the usefulness of plasma zinc levels in assessing prognosis after myocardial infarction, prognosis in group 1 was judged by the severity of arrhythmias, the number of days spent in hospital after myocardial infarction, and by a coronary prognostic index (Norris *et al.*, 1970).

Arrhythmias were graded on an arbitrary scale from 1 to 5. Grade 1 represented trivial or no arrhythmia (32 cases), grade 2 a significant arrhythmia requiring treatment (30 cases), grade 3 a potentially life-threatening arrhythmia (8 cases), grade 4 cardiac arrest successfully treated (8 cases), and grade 5 death (10 cases). There is a downward trend in the mean minimum zinc level with increasing severity of arrhythmia (Fig.), and on overall analysis this correlation is highly significant.

For those patients with myocardial infarction who survived, the correlation between the minimum plasma zinc level and the duration in hospital was also highly significant ($P < 0.001$).

There was a highly significant correlation between the minimum plasma zinc level and an accepted coronary prognostic index (Norris *et al.*, 1970).

Discussion

Our results confirm the findings of previous workers (Wacker *et al.*, 1956; Halsted and Smith, 1970; Lindeman *et al.*, 1973; Handjani *et al.*, 1974) that plasma zinc falls in myocardial infarction. Myocardial necrosis can, therefore, be distinguished from ischaemia and non-cardiac chest pain.

Although plasma zinc changes lack specificity in general, in the context of a coronary care unit

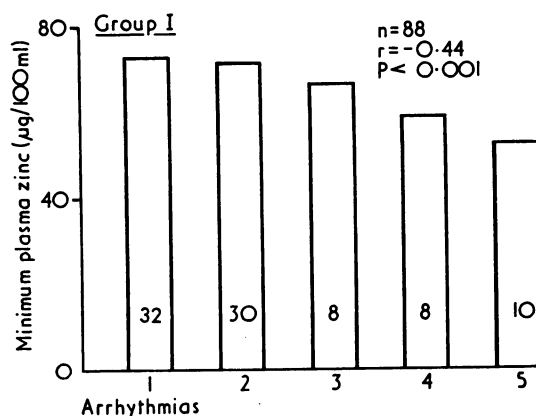


FIG. Minimum plasma zinc and arrhythmias. ($1 \mu\text{g}/100 \text{ ml} \approx 0.153 \mu\text{mol/l}$)

these may be taken as a reliable test of infarction.

The specificity of plasma zinc estimation as a diagnostic test in myocardial infarction may be estimated by using Bayes' theorem (Katz, 1974). In patients admitted to our coronary care unit the probability of a positive zinc test (minimum plasma zinc below $75 \mu\text{g}/100 \text{ ml}$ with a fall in the first three days) representing myocardial infarction was 80 per cent.

The minimum plasma zinc showed a significant correlation with both enzymes and clinical indices of prognosis. The magnitude of the change in plasma zinc showed a significant correlation with the plasma enzymes only. We conclude that the minimum plasma zinc level is the most clinically useful measure of plasma zinc changes in acute myocardial infarction.

The correlation between change in plasma zinc and enzymes was good for LDH, fair for CK, and poor for AST. Since LDH is a zinc-containing metalloenzyme its closer correlation is understandable. The CK is often altered for non-cardiac reasons, e.g. intramuscular injection (Scott *et al.*, 1974) and hence was less closely related. The poor correlation with AST has no obvious explanation.

The time course of changes in plasma zinc is particularly fortunate for the diagnosis of myocardial infarction. Since the level falls in the first few days and does not return to normal levels for $1\frac{1}{2}$ to 2 weeks, it enables both acute and recent infarcts to be detected.

The measurement of plasma zinc is technically simple, and cheaper than many routine enzyme tests, provided a trace metal laboratory is available. Plasma zinc has the added advantage of not being altered by minor tissue damage or by intramuscular injections.

The precise reason why plasma zinc falls in acute myocardial infarction is still unknown. Plasma zinc has been shown to fall after administration of steroids (Flynn *et al.*, 1971). It is possible that the fall after myocardial infarction may be steroid-related, though the peak in plasma cortisol occurs within the first 12 hours (Bailey, Abernethy, and Beaven, 1967), while the fall in plasma zinc takes somewhat longer.

Studies of heart muscle have shown no real change in the zinc concentration of infarcted muscle compared with normal myocardium (Chipperfield and Chipperfield, 1973). However, increases have been shown in the subcellular fractions where synthesis and storage of enzymes occurs, and it is thought that this might be the result of an increase in enzyme synthesis, in an effort to promote repair (Lindeman *et al.*, 1973). This redistribution of zinc cannot account for the zinc that disappears from the plasma which is thought to be taken up by the liver, and perhaps by other visceral organs also (Lindeman *et al.*, 1973). During stress there is release of a humoral factor produced by polymorphs (leucocyte endogenous mediator, or LEM), which depresses plasma zinc levels, and increases zinc uptake by the liver (Pekarek, Wannemacher, and Beisel, 1972). An alpha₂-macroglobulin containing a large amount of zinc has been isolated, and proposed as a transport protein (McBean *et al.*, 1974). The level of this carrier protein is raised in myocardial infarction and other states associated with a fall in plasma zinc.

The data presented in this study indicate that a fall in plasma zinc is a useful empirical diagnostic test for myocardial infarction. The extent of the fall correlates well with the rise of plasma enzymes, and also with some clinical estimates of prognosis.

The postulated importance of zinc in wound healing even if only in zinc-deficient states (Henkin, 1974) suggests that zinc may play a more fundamental role in recovery after myocardial infarction. Thus the intriguing question arises as to whether administration of zinc to patients with myocardial infarction might improve prognosis.

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