Calcium and Myocardial Infarction

D. JACOBS

SUMMARY

Serum calcium levels tend to be low in patients with acute myocardial infarction. Urinary excretion of calcium tended to be even lower in these patients, and particularly so in men. It is suggested that excessive amounts of calcium are deposited in the arteries in patients with coronary heart disease. Possible mechanisms relevant to the racial incidence of myocardial infarction are discussed. A concept for further research is proposed.

S. Afr. Med. J., **48**, 523 (1974).

HISTORICAL

'On October the 16th, 1793 . . . meeting with some things which irritated his mind . . . he gave a deep groan and dropt down dead.

Upon inspecting the body after death . . . the cartilages of the ribs had, in many places, become bone . . . The coronary arteries . . . in the state of bony tubes were with difficulty divided by the knife'.

Home: *Life of John Hunter.*[1]

Previous personal[2,3] and other studies have indicated that people with certain characteristics form a high-risk group in which the chances of sustaining myocardial infarction are higher than those of the general population. The significance of these various characteristics, however, remains controversial. Associated risk factors apart, attention has been directed at other possible factors — one of these being calcium. The possibility of hypercalcaemia being a factor in the development of coronary atherosclerosis has been considered. This was based on a hypothetical correlation between sunshine exposure, vitamin D metabolism, the relationship to calcium turnover, and the high incidence of myocardial infarction among young men in Southern Africa.

In a small series of patients, serum calcium levels were, however, found to be lower than the accepted normal mean.[2] The present investigation was undertaken to study further the relationship, if any, between calcium and myocardial infarction.

PATIENTS AND METHODS

Seventy-five consecutive cases of acute myocardial infarction, treated in the Medical Unit of Discoverers' Memorial Hospital, Florida, were studied. The patients were all adult White South Africans. The criteria used for the diagnosis of myocardial infarction were: the clinical history and examination, with electrocardiographic evidence of pathological Q waves, ST-segment changes, later T-wave inversion, a falling R wave in the praecordial leads, complete left bundle-branch block and, when necessary, significant and transient elevation of serum lactate dehydrogenase and serum glutamic oxalo-acetic acid transaminase levels.

In addition, a group of adult Black inpatients, without evidence of coronary heart disease, were studied in order to compare serum with urinary calcium ratios.

For purposes of this study, the following normal ranges for adults of both sexes, as listed by the South African Institute for Medical Research in Johannesburg, were used:

Serum calcium	4,5 — 5,3 mEq/L	(mean 5,0)
	9,0 —10,6 mg/100 ml	
Serum CO_2 content	23 — 32 mEq/L	
Serum inorganic phosphorus	2,5 — 4,5 mg/100 ml	
Whole blood urea	15 — 40 mg/100 ml	

The normal range for urine calcium used was 141,1 — 364,9 mg/24 h.[4]

Blood samples were taken on the first prothrombin index day (4th day after admission) and occasionally later. Collection of 24-hour urine samples for calcium commenced on the same day.

RESULTS

Age and Sex

The 75 patients comprised 33 men and 42 women. The age range for the men was 29 - 82 years and for the women 44 - 87 years. In the under-50 age group men predominated. From the 6th decade there were more women. These differences are reflected in a skewed frequency polygon (Fig. 1).

Serum Calcium Levels

These levels ranged from 3,9 to 6,0 mEq/L for the men and from 3,7 to 5,3 mEq/L for the women. Only 2 of the 33 men had levels over 5,3 mEq/L and none of the 42 women were above this upper level of normality. Sixty-six of the 75 patients had levels at or below the accepted normal mean of 5,0 mEq/L (Fig. 2).

Serum calcium levels relative to both age and sex showed no statistically significant difference between the respective age groups 64 years and under and 65 years and over. There was, however, a definite trend suggesting that for both sexes the higher age group had higher serum calcium levels. This is shown in Table I. Expressed

Discoverers' Memorial Hospital, Florida, Transvaal
D. JACOBS, M.D., F.R.C.P.

Date received: 27 August 1973.

TABLE I. SERUM CALCIUM LEVELS RELATIVE TO AGE AND SEX IN 75 PATIENTS WITH MYOCARDIAL INFARCTION

⩽ 64 years						⩾ 65 years					
Males		Females		Both		Males		Females		Both	
No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean
21	4,6	16	4,57	37	4,6	12	4,8	26	4,68	38	4,7

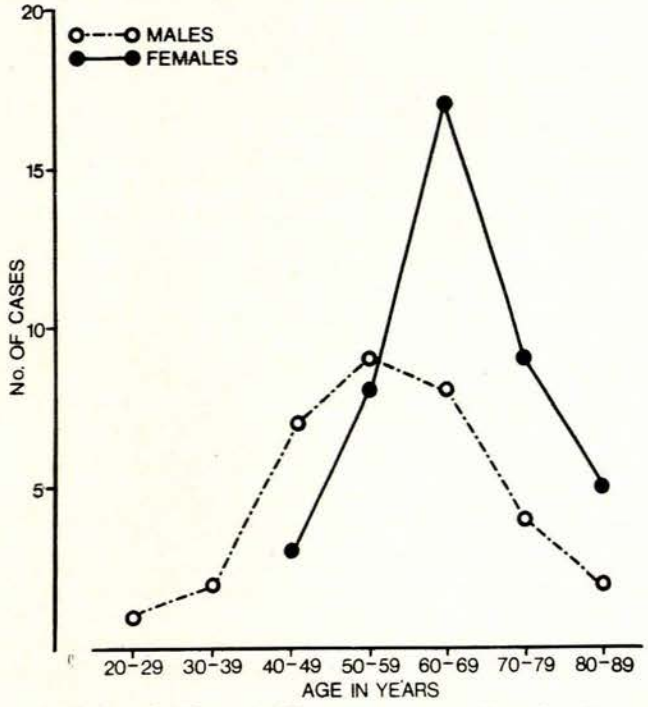

Fig. 1. Age incidence in 75 cases of myocardial infarction.

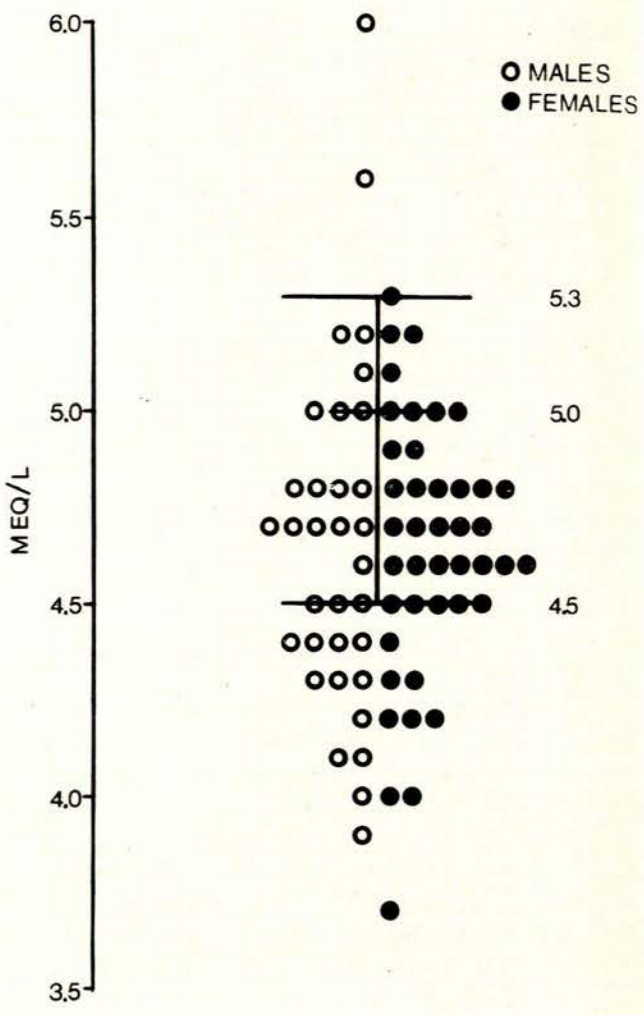

Fig. 2. Serum calcium levels in myocardial infarction.

in terms of mean and standard error, the trend to higher levels in the older group was even more obvious (Fig. 3).

In the 37 patients of both sexes aged 64 years and under, the mean was 4,6 mEq/L with standard error 0,06. For the 38 patients 65 years and over, the mean was 4,7 mEq/L with standard error 0,064. Student's *t*-test was applied to the actual values and showed that the difference in the means was only significant to the 0,1 - 0,2 level (10 - 20%) with 73 degrees of freedom. This test failed to show a statistically significant difference, but showed, nevertheless, a trend favouring higher levels in the older subjects.

Urine Calcium Levels

It was possible to measure the urinary output of calcium over 24 hours in 40 patients. The urinary calcium was below the minimal normal in 32 (80%). In 27 of these 40 patients, where serum levels were within the normal range of 4,5 - 5,3 mEq/L, the urine levels were below the minimal normal in 20 (74%) (Fig. 4).

The mean urine calcium levels were lower in the 65-year-and-over age group, and while these results failed to reach statistical significance, there was a definite trend towards lower levels in this older group. (Table II). Expressed in terms of means and standard error, this decrease in the older groups became even more obvious (Fig. 5).

TABLE II. TWENTY-FOUR-HOUR URINE CALCIUM LEVELS RELATIVE TO AGE IN 75 PATIENTS WITH MYOCARDIAL INFARCTION

⩽ 64 years		⩾ 65 years		All ages	
No.	Mean	No.	Mean	No.	Mean
18	122,9	22	104,3	40	112,6

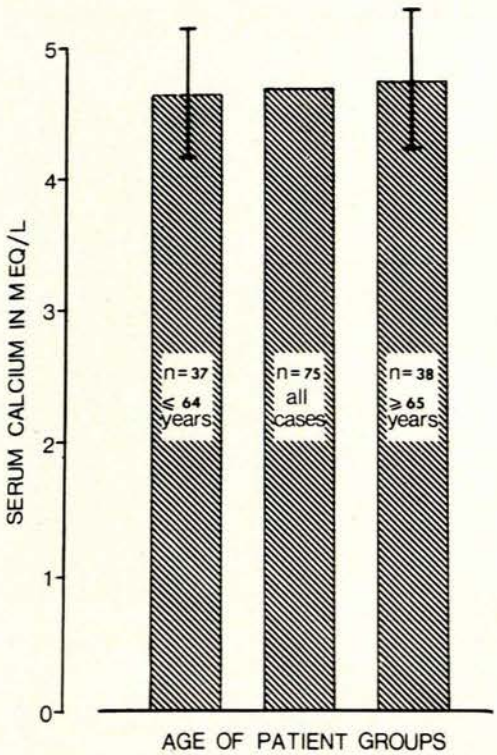

Fig. 3. Serum calcium in myocardial infarction (means and standard error relative to age).

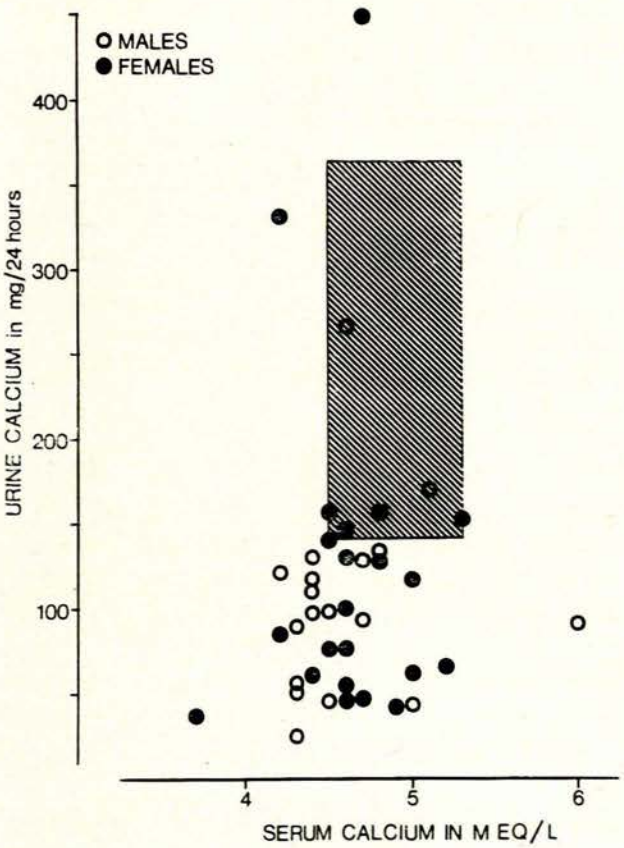

Fig. 4. Serum and urine calcium levels in myocardial infarction.

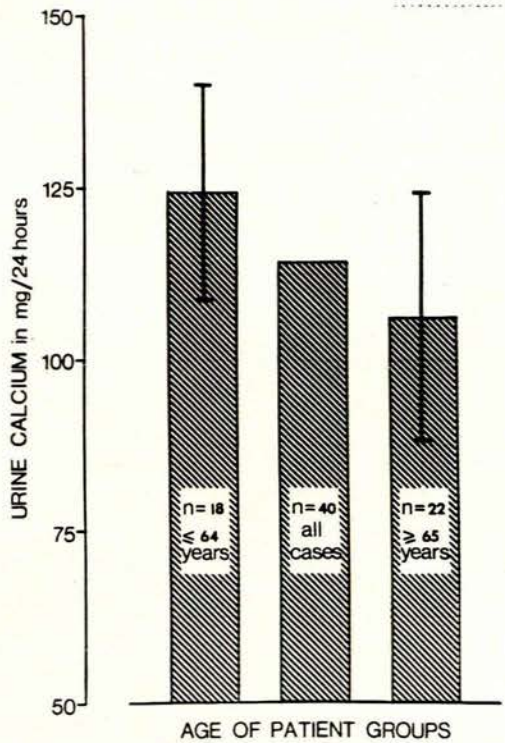

Fig. 5. Urine calcium in myocardial infarction (means and standard error relative to age).

In the entire series, by comparing the sexes, it was found that the 33 men had slightly higher serum calcium levels than the 42 women (Table I). In 40 patients (18 men, 22 women), where both blood and urine figures were available, no sexual difference with regard to serum levels was found, although urine levels were lower in males (Table III). This failure to detect a difference in the serum levels of these men and women may have been due to sample size. This same male group was, however, a decade younger than the female group. The data relevant to serum and urine levels in these 40 patients were further analysed to determine whether there was a statistical relationship between serum levels and the amount that passed into the urine. A chi-square test was applied to the actual values and showed the following: $\chi^2_{2\,df}$ 18,96. This result was highly significant. Further confirmation was obtained by a 2 × 2 contingency table. These analyses show that even with normal serum levels the urine calcium was low, and this was applicable mainly to men but also to women.

There are several factors that can influence serum calcium levels and it was possible to measure some of these objectively.

Serum Inorganic Phosphorus

Serum inorganic phosphorus was correlated against calcium levels in 10 consecutive patients, and the results failed to show any inverse relationship between the two ions (Fig. 6).

TABLE III. MEAN SERUM AND URINE CALCIUM LEVELS RELATIVE TO AGE AND SEX IN 40 PATIENTS WITH MYOCARDIAL INFARCTION

Females (22)			Males (18)			Both sexes (40)		
Age (yrs)	Serum (mEq/L)	Urine (mg/100 ml)	Age (yrs)	Serum (mEq/L)	Urine (mg/100 ml)	Age (yrs)	Serum (mEq/L)	Urine (mg/100 ml)
68,09	**4,64**	**119,91**	**59,72**	**4,61**	**103,83**	**64,33**	**4,62**	**112,67**

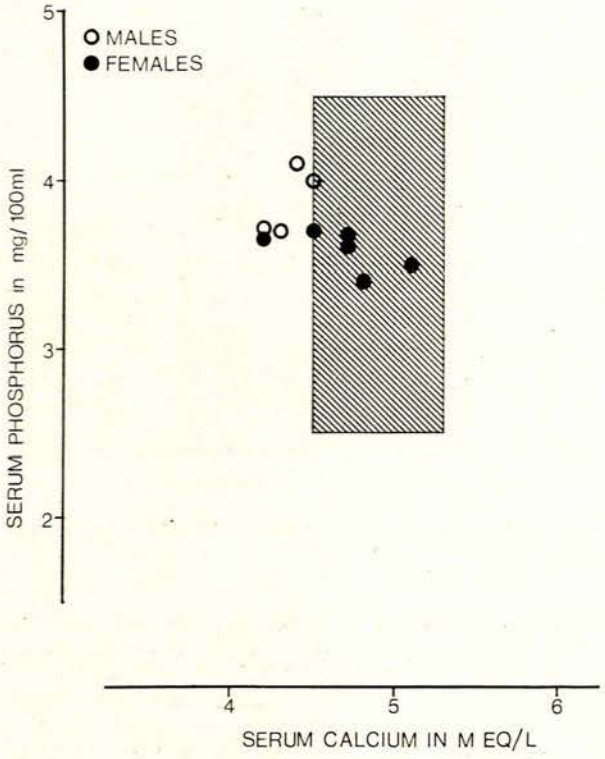

Fig. 6. Serum inorganic phosphorus and calcium levels in myocardial infarction.

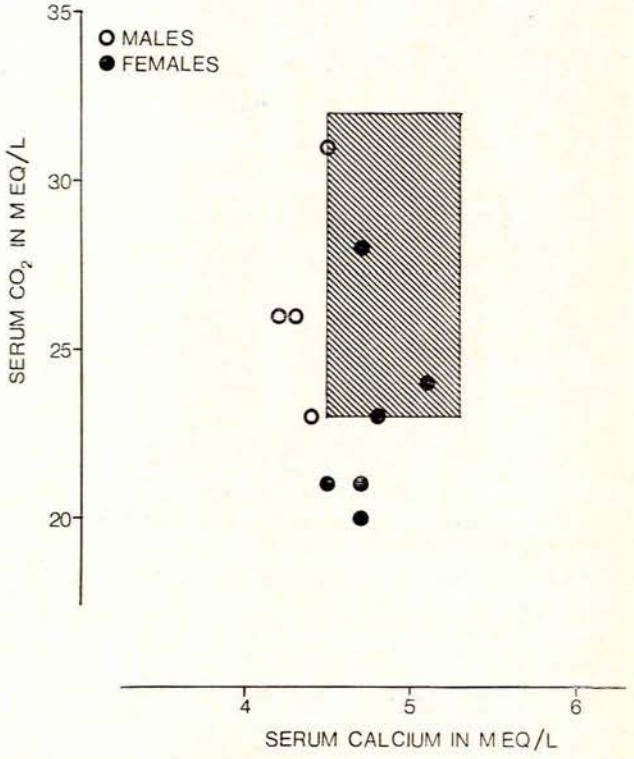

Fig. 7. Serum CO_2 and calcium levels in myocardial infarction.

Plasma proteins and blood urea were also measured in 10 consecutive patients, and in all of these both the plasma protein and urea levels were normal, and no relationship could be found to the serum calcium.

Serum CO_2 Content

Serum CO_2 content likewise failed to show any relationship. Some of the patients had low calcium levels and others low CO_2, but the scatter was too great (Fig. 7).

Control Subjects

These subjects consisted of 5 Black inpatients in whom there was no clinical or electrocardiographic evidence of coronary heart disease. Their blood levels of calcium were reasonably normal, but urine levels were remarkably low (Table IV). After these remarkably low excretion values in the Black patients, it was decided that this group was not a satisfactory control.

TABLE IV. SERUM AND URINE CALCIUM LEVELS IN BLACK INPATIENTS (CONTROLS)

Sex	Serum (mEq/L)	24-hour urine (mg/100 ml)
Male	**5,8**	**69**
Male	**4,5**	**28**
Female	**4,4**	**21**
Female	**4,6**	**106**
Female	**4,5**	**48**

DISCUSSION

Most discussions about the pathogenesis of coronary heart disease evolve around the significance of known associated risk factors, such as cholesterol. Pathologically, the vascular lesions are sclerotic and calcific, yet the possible role of calcium itself is rarely mentioned.

A previous study of serum calcium levels in myocardial infarction showed a tendency to low serum calcium levels

rather than the expected hypercalcaemia.[2] The results of the present series confirm that patients with acute myocardial infarction have either normal or low serum calcium levels (Figs 2 and 3). In addition, urinary excretion of calcium by these subjects is distinctly lower than the accepted normal range. One possible explanation for this is that the values accepted for the normal range do not apply to this group of adult White South Africans. These normal values may be questioned because they were based on the testing of only 8 subjects.[4] Possibly, more studies would show the normal range to be lower. Alternatively, it may be that patients with acute myocardial infarction, or those developing coronary atherosclerosis, are not excreting calcium in the urine. As a theoretical corollary, perhaps they are super-saturating their arteries with calcium. There is obviously a need to test a control group. This was not done in the present series because it was impossible to find a group of adult White subjects in whom coronary atherosclerosis could confidently be excluded. The absence of acute myocardial infarction cannot serve as an adequate control. It is believed that for practical purposes all adult Whites suffer from atherosclerosis to a greater or lesser degree.

Five adult Black inpatients were studied and they had no clinical or electrocardiographic evidence of coronary atherosclerosis: this, of course, is a very crude way of assessing the presence or absence of arterial disease. In these 5 patients serum levels were adequate, but urine levels were remarkably low (Table IV). Urine volumes were adequate and the estimations were performed by the same laboratory that measured the White group.

The 24-hour calcium intake of White patients with myocardial infarction in this hospital unit has been estimated to average 1,12 g in an 7 200-kJ diet. The average diet of the Black patients supplies 8 000 kJ and 0,67 g of calcium intake per 24 hours. The amount of calcium in the water supply is 35 parts per million, which represents a negligible extra amount, and which is, in any event, equal for both racial groups. The diet of the Black patients has been designed to be as nutritious as possible and, at the same time, to be as palatable and as near the standard diet that this group prefers.

It was because of the remarkably low urine figures in the Blacks that this control group was abandoned. It was realised that they were not a suitable control group.

It is possible that the chronic administration, over years, of a lower calcium diet, affords protection to the Blacks. Despite a reduced total body pool, blood levels may be maintained by homeostasis, at the expense of diminishing levels elsewhere, such as in the arterial walls. The increased intake by White patients may lead to greater or earlier arterial calcification.

With regard to sex differences, the male group excreted less calcium than the female group. Their peak incidence of infarction was a decade earlier. Possibly, calcium is transported into the arteries of men, thereby causing them to have coronary episodes more often and at an earlier age than occurs with women.

A possible relationship between vitamin D metabolism, calcium and the difference in incidence of myocardial infarction between White and Black South Africans has previously been questioned. Possibly, Blacks are protected by a differing vitamin D exposure? This difference may occur in the skin or at another level. Evidence has also been presented to suggest that an alteration of vitamin D metabolism in the liver, as a result of microsomal enzyme induction, may be an important factor in the development of hypocalcaemia.[6]

Calcium metabolism and serum calcium levels depend fundamentally upon intake, absorption, parathyroid activity, concentration of plasma proteins, plasma phosphate levels, plasma concentration of H^+ ions, and renal function. Intake and urinary loss were assessed. Plasma protein concentration, serum inorganic phosphorus and renal function, as judged by blood urea, were measured in 10 patients and found to be normal. Serum CO_2 content was also measured in 10 patients because alkalaemia can cause tetany, although it is realised that serum calcium levels should not drop. There was no clear-cut correlation. The other influencing physiological factors would need to be measured in order to evaluate further the present hypotheses, although it would seem unlikely that they are significant.

REFERENCES

1. Home, Sir Everard (1796): *Life of John Hunter* (Treatise on the Blood, Inflammation and Gunshot Wounds), *in* Major, R. H. ed. (1932): *Classic Descriptions of Disease*, 3rd ed. Springfield, Ill.: C. C. Thomas.
2. Jacobs, D. (1971): S. Afr. Med. J., **45**, 275.
3. *Idem* (1972): *Ibid.*, **46**, 367.
4. Weber, R. J. (1937): Proc. Soc. Exp. Biol. (N.Y.), **37**, 59.
5. Gamble, J. L. (1954): *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*, 6th ed. Cambridge, Mass.: Harvard University Press.
6. Hunter, J., Maxwell, J. D., Stewart, D. A., Parsons, V. and Williams, R. (1971): Brit. Med. J., **4**, 202.