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# Relation of serum calcium concentration to metabolic risk factors for cardiovascular disease

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## Abstract

**Data from a health screening survey with over 18 000 adult participants were used to determine the relations between serum calcium concentration and the cardiovascular risk factors hypertension, hyperglycaemia, and hyperlipidaemia. Blood pressure and serum glucose and cholesterol concentrations were all positively related to each other independent of age, sex, kidney function, and obesity. Similar relations between the risk factors were found in subjects with hypertension or hyperglycaemia independent of the degree of overweight. These results suggested that there might be a metabolic syndrome of cardiovascular risk factors. Serum calcium concentration was positively related to systolic and diastolic blood pressures and serum glucose and cholesterol concentrations. Thus a common feature in the syndrome is an increased serum calcium concentration. The relations between serum calcium concentrations and the cardiovascular risk factors were not limited to the upper parts of the distribution, being seen over a wide range.**

**Changes in calcium metabolism seem to be related to a metabolic syndrome of hypertension, impaired glucose tolerance, and hyperlipidaemia.**

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## Introduction

The calcium ion is an essential regulator in many homoeostatic systems, including vascular tone, hormone secretion, and intermediary metabolism.[1] Calcium metabolism is reportedly altered in both hypertension[2] and diabetes mellitus,[3] and a pathogenetic role for calcium in the aetiology of hypertension has been suggested.[4] Hypertension, hyperglycaemia, and hyperlipidaemia are all well known risk factors for the development of cardiovascular disease,[5-7] and their coexistence might therefore be particularly important. We investigated interrelations between these risk factors and their relations to serum calcium concentration using data from a large health screening survey.

## Subjects and methods

During 1969-70 all 24 171 inhabitants aged over 25 in a central district of Gävle, Sweden, were invited to participate in a health screening survey; 77% of the invited population took part (8416 men and 10 127 women). The non-participants were mainly from the youngest (25-35) and oldest (>85) age groups. The studied sample was considered to be representative for the ages 35-85 and large enough for us to study interrelations between metabolic variables. The aims of the health screening were to find undetected diseases and to evaluate the effects of such screening. The participants were asked to attend according to home address rather than by age or sex.

A venous blood sample was taken, usually in the afternoon after four hours of fasting, and analysed with a Technicon autoanalyser SMAC 12/60 (Mark Technicon Corp, USA) for serum glucose, cholesterol, calcium, and albumin concentrations and blood urea nitrogen concentration. Particular attempts were made to eliminate sources of error in the measurements. The results were compared with those obtained from standard samples (every fifth to 10th sample) from a large pool of serum calibrated every second week against a commercial reference. The serum calcium concentrations in the study were all adjusted for the serum albumin concentration according to the formula: calcium (adjusted)=calcium (analysed)−0·0077 (albumin−43·3), where 0·0077 was the determination coefficient of the regression analysis and 43·3 the mean albumin concentration in the population.[8]

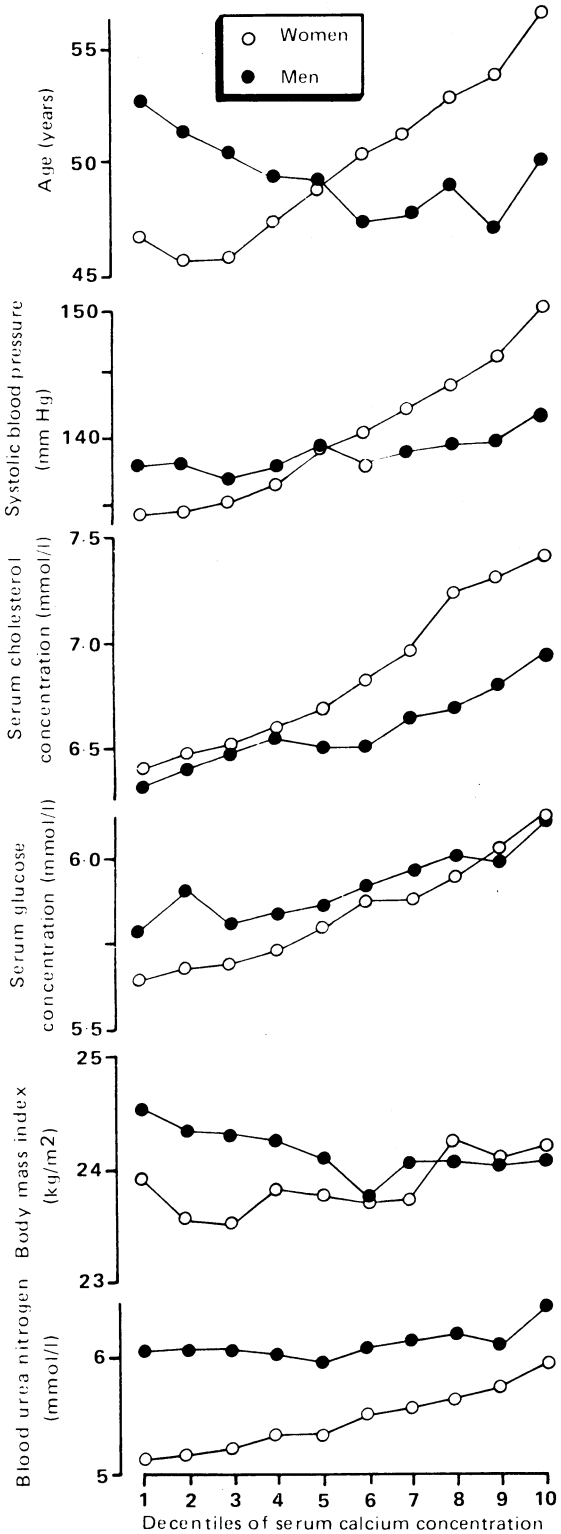
Body mass index, used as an index of obesity, was defined as weight (kg)/height (m)$^2$. Blood pressure was measured in the supine position after 10 minutes' rest

with a mercury sphygmomanometer. The diastolic blood pressure was read at phase V of the Korotkoff sounds. To determine metabolic disturbances in hypertension we studied only subjects who were not taking treatment as antihypertensive drugs may cause metabolic alterations.[9]

Two groups of subjects with hypertension were defined. The first group comprised people with systolic blood pressure >160 mm Hg and diastolic blood pressure >105 mm Hg; 781 such subjects who were not taking antihypertensive treatment were found. The second group, of subjects with milder hypertension, comprised those with systolic blood pressure >160 mm Hg and diastolic pressure 95-105 mm Hg; 965 such subjects not taking antihypertensive treatment were found. For each subject two people matched for age and sex and with normal blood pressure (<160/95 mm Hg) were selected from the screening programme to serve in the two control groups. The controls were chosen so that the period between the date of birth of the index person and the two controls was as short as possible. The difference was in most cases only a matter of days.

Two groups of subjects with raised serum glucose concentrations were also defined. Subjects with concentrations >8·3 mmol/l were considered to have diabetes mellitus and those with concentrations of 6·7-8·3 mmol/l to have impaired glucose tolerance or mild diabetes mellitus. For each of the subjects in these two groups two controls were selected from the screening programme. All controls were matched for age and sex and had normal serum glucose concentrations (<6·1 mmol/l).

All data were put on to computer, and the statistical package for the social sciences (SPSS; IBM, United States) was used for analysis. Pearson's correlation coefficients were used for the univariate correlations. One way or two way analysis of variance was used to compare means between groups; two way analysis was used when the groups were matched for age and sex. The $\chi^2$ test was used to compare proportions between groups. Multiple regression analysis was used to evaluate whether the relations between cardiovascular risk factors and serum calcium concentration were independent of age, body mass index, and blood urea nitrogen concentration. Two tailed significance values are given.




*Relation between decentiles of serum calcium concentration and age, systolic blood pressure, serum cholesterol and glucose concentrations, body mass index, and kidney function. Maximum SE: 0·018 for age, 0·029 for systolic blood pressure, 0·0014 for serum cholesterol concentration, 0·0015 for serum glucose concentration, 0·004 for body mass index, and 0·0017 for blood urea nitrogen concentration. (Graph for diastolic blood pressure (not shown) closely similar to that for systolic blood pressure)*

## Results

Table I shows the means of the variables studied in men and women. There was no striking difference in age, blood pressure, body mass index, or serum glucose concentrations between the sexes. Blood urea nitrogen concentration was higher in men and serum cholesterol concentration higher in women (p<0·001). The distribution of serum calcium concentration was shifted slightly to higher values in women (table II). Furthermore, the relation between calcium concentration and age differed between men and women as the concentration increased with age in women but tended to fall in men (figure). Both systolic and diastolic blood pressures were raised with higher serum calcium concentrations in both sexes, the relation being more pronounced in women. The same pattern was seen for serum cholesterol and glucose concentrations. Body mass index tended to rise slightly with increasing serum calcium concentration in women and to decrease slightly in men.

TABLE I—*Mean (SD) values of variables studied in entire population*

| | Men (n=8416) | Women (n=10 127) |
|---|---|---|
| Age (years) | 49·4 (14) | 50·0 (14) |
| Blood pressure (mm Hg): | | |
| Systolic | 138·0 (20) | 140·0 (26) |
| Diastolic | 85·5 (12) | 84·6 (13) |
| Serum calcium (mmol/l) | 2·44 (0·10) | 2·46 (0·11) |
| Body mass index (kg/m²) | 24·2 (3·1) | 23·4 (3·8) |
| Blood urea nitrogen (mmol/l) | 6·2 (1·5) | 5·5 (1·5) |
| Serum glucose (mmol/l) | 5·9 (1·1) | 5·8 (1·1) |
| Serum cholesterol (mmol/l) | 6·6 (1·2) | 6·9 (1·3) |

TABLE II—*Mean value (mmol/l) in each decentile of serum calcium concentration in men and women*

| | Decentile | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th | 10th |
| Men | 2·27 | 2·35 | 2·37 | 2·40 | 2·43 | 2·45 | 2·47 | 2·49 | 2·54 | 2·63 |
| Women | 2·28 | 2·36 | 2·39 | 2·42 | 2·45 | 2·47 | 2·49 | 2·52 | 2·57 | 2·67 |

The univariate correlation coefficients for the relations between serum calcium concentration and the variables described above were highly significant (table III). Multiple regression analysis showed that there was a significant ($p<0.001$) positive relation between serum calcium concentration and systolic and diastolic blood pressures and serum cholesterol and glucose concentrations in both sexes even when the effects of age, body mass index, and blood urea nitrogen concentration were considered. Multiple regression analysis indicated that the biological variation of serum calcium concentration (SD 2·0) could explain a variation in systolic blood pressure of around 8 mm Hg, diastolic blood pressure of 4·6 mm Hg, and serum glucose and cholesterol concentrations of 0·4 mmol/l and 0·7 mmol/l respectively after correction for age, body mass index, and blood urea nitrogen concentration. When the effects of serum calcium concentration and body mass index on the same risk factors were compared the effect of serum calcium concentration was less than half that of body mass index on blood pressure but was slightly greater than that of body mass index on serum glucose and cholesterol concentrations.

Both systolic and diastolic blood pressures in men and women showed a significant positive correlation with age, body mass index, and blood urea nitrogen and serum glucose cholesterol concentrations (table III). Serum glucose and cholesterol concentrations also showed a significant ($p<0.001$) positive relation with blood pressure in both sexes after adjustment for age, body mass index, and blood urea nitrogen concentration in multiple regression analysis.

When subjects with systolic blood pressure >160 mm Hg and diastolic blood pressure >105 mm Hg were compared with their matched controls body mass index and serum calcium, glucose, and cholesterol concentrations were all significantly higher in the subjects ($p<0.001$) (table IV). The same pattern was seen in the group with mild hypertension. The differences between hypertensive subjects and controls were still significant in a covariance analysis adjusting for the higher body mass index seen in the hypertensive groups.

Serum glucose concentration showed a significant positive correlation with age, body mass index, and serum cholesterol concentration in both sexes (table III). When correction was made for age, blood urea nitrogen concentration, and body mass index in the multiple regression analysis serum glucose concentration was still significantly related ($p<0.001$) to serum cholesterol concentration in men but not women.

Subjects with hyperglycaemia (glucose concentration >8·3 mmol/l) had significantly higher blood pressure, serum calcium concentration, and body mass index than their controls; a tendency to higher serum cholesterol concentrations was also found (table V). Antihypertensive treatment was more common among the hyperglycaemic subjects than their controls. The group with mild hyperglycaemia (serum glucose concentration 6·7-8·3 mmol/l) had significantly higher blood pressure, body mass index, and serum cholesterol and calcium concentration than their controls (table IV). The subjects in this group were also more commonly treated with antihypertensive drugs than their controls. When covariance analysis was applied, correcting for the differences in body mass index and antihypertensive treatment between the hyperglycaemic subjects and controls, the differences in blood pressure and serum calcium and cholesterol concentrations remained significant.

TABLE III—*Univariate correlation coefficients. Figures in roman type apply to women; those in italic type apply to men*

| | Age | Blood pressure: Systolic | Blood pressure: Diastolic | Serum calcium | Body mass index | Blood urea nitrogen | Serum glucose | Serum cholesterol |
|---|---|---|---|---|---|---|---|---|
| Age | | 0·54 | 0·48 | 0·22 | 0·31 | 0·36 | 0·27 | 0·42 |
| Blood pressure: | | | | | | | | |
| Systolic | *0·34* | | 0·79 | 0·20 | 0·33 | 0·20 | 0·26 | 0·29 |
| Diastolic | *0·30* | *0·70* | | 0·18 | 0·36 | 0·14 | 0·20 | 0·29 |
| Serum calcium | *−0·07* | *0·08* | *0·06* | | 0·04 | 0·16 | 0·14 | 0·21 |
| Body mass index | *0·12* | *0·21* | *0·32* | *−0·03* | | 0·10 | 0·14 | 0·19 |
| Blood urea nitrogen | *0·20* | *0·06* | *0·03* | *0·06* | *0·03* | | 0·15 | 0·15 |
| Serum glucose | *0·15* | *0·17* | *0·09* | *0·10* | *0·06* | *0·06* | | 0·12 |
| Serum cholesterol | *0·15* | *0·11* | *0·17* | *0·13* | *0·19* | *0·07* | *0·06* | |

$p<0.001$ for all correlation coefficients except $r=0.03$, which gives $p<0.01$.

TABLE IV—*Comparison of subjects with raised blood pressure with controls. Values expressed as means (SD)*

| | Subjects with severe hypertension and their controls | | | Subjects with mild hypertension and their controls | | |
|---|---|---|---|---|---|---|
| | Subjects with blood pressure >160/>105 mm Hg | Controls | p Value | Subjects with blood pressure >160/95-105 mm Hg | Controls | p Value |
| No | 781* | 1562* | | 965† | 1930† | |
| Age (years) | 59·7 (10·7) | | | 61·1 (11·0) | | |
| Blood pressure (mm Hg): | | | | | | |
| Systolic | 187 (20·0) | 134 (14·0) | | 173 (13·0) | 134 (14) | |
| Diastolic | 112 (7·8) | 81·1 (7·2) | | 99·0 (2·5) | 81·7 (7·3) | |
| Body mass index (kg/m²) | 26·1 (4·1) | 24·2 (3·4) | 0·001 | 25·3 (3·7) | 24·0 (3·4) | 0·001 |
| Blood urea nitrogen (mmol/l) | 5·9 (1·5) | 6·1 (1·4) | 0·001 | 5·9 (1·4) | 6·1 (1·3) | 0·001 |
| Serum calcium (mmol/l) | 2·47 (0·12) | 2·45 (0·11) | 0·001 | 2·47 (0·11) | 2·45 (0·11) | 0·001 |
| Serum glucose (mmol/l) | 6·2 (1·2) | 5·8 (1·0) | 0·001 | 6·3 (1·5) | 5·9 (1·0) | 0·001 |
| Serum cholesterol (mmol/l) | 7·3 (1·3) | 7·0 (1·2) | 0·001 | 7·2 (1·2) | 7·0 (1·2) | 0·001 |

*56% Were men. †61% Were men.

TABLE V—*Comparison of subjects with hyperglycaemia with controls. Values expressed as means (SD) unless otherwise stated*

| | Subjects with severe hyperglycaemia and their controls | | | Subjects with mild hyperglycaemia and their controls | | |
|---|---|---|---|---|---|---|
| | Subjects with serum glucose >8·3 mmol/l | Controls | p Value | Subjects with serum glucose 6·7-8·3 mmol/l | Controls | p Value |
| No | 263* | 526* | | 1142* | 2284* | |
| Age (years) | 62·1 (12) | 62·1 | | 58·3 (14) | 58·3 | |
| Serum glucose (mmol/l) | 12·5 (3·7) | 5·6 (0·4) | | 7·0 (0·4) | 5·6 (0·3) | |
| Blood pressure (mm Hg): | | | | | | |
| Systolic | 160 (26·0) | 147 (26·0) | 0·001 | 155 (26·0) | 146 (26·0) | 0·001 |
| Diastolic | 91·7 (14·0) | 87·4 (13) | 0·001 | 90·6 (13·0) | 87·3 (12·0) | 0·001 |
| Body mass index (kg/m²) | 25·5 (4·1) | 24·2 (3·6) | 0·001 | 25·0 (4·0) | 24·2 (3·4) | 0·001 |
| Blood urea nitrogen (mmol/l) | 6·5 (1·8) | 6·1 (1·6) | 0·01 | 6·2 (1·7) | 6·1 (1·6) | Not significant |
| Serum calcium (mmol/l) | 2·49 (0·12) | 2·45 (0·11) | 0·001 | 2·49 (0·11) | 2·45 (0·11) | 0·001 |
| Serum cholesterol (mmol/l) | 7·1 (1·6) | 7·0 (1·3) | Not significant | 7·1 1·3) | 7·0 (1·3) | 0·006 |
| No (%) receiving antihypertensive treatment | 63 (24) | 49 (9) | 0·001 | 171 (15) | 203 (9) | 0·001 |

*33% Were men.

## Discussion

This study found positive relations between blood pressure and serum glucose and cholesterol concentrations, all of which were independently associated with serum calcium concentrations. Furthermore, similar relations between risk factors were found in hypertensive and hyperglycaemic subjects. Based on these observations we suggest that there is a metabolic syndrome comprising hypertension and impaired glucose and lipid metabolism. Some aspects of this metabolic syndrome of cardiovascular risk factors have been described before. Hypertension has been associated with impaired glucose tolerance, high insulin concentrations, and insulin resistance.[10-14] Hyperlipidaemia, in particular hypertriglyceridaemia, has also been described in hypertensive subjects.[10 15] Impaired lipid metabolism as well as a high prevalence of hypertension have been found in people with impaired glucose tolerance and diabetes mellitus.[12 16 17] Positive relations between these cardiovascular risk factors have also been described in population studies.[18-20]

The relations between the metabolic risk factors were considered together and the effect of other important characteristics such as age, sex, obesity, and kidney function excluded by multiple regression analysis. Other relations in the syndrome are therefore likely to exist. One putative connecting link in the metabolic syndrome is hyperinsulinaemia. Tissue resistance to insulin and hyperinsulinaemia are common in both hypertension and diabetes mellitus.[12 14 21] Insulin also promotes hyperlipidaemia, especially hypertriglyceridaemia,[16] and causes sodium retention,[22] which might raise blood pressure. Insulin also increases sympathetic nerve activity,[23] which would influence all the risk factors in the metabolic syndrome.

Something else common to the risk factors in this syndrome may be a disturbance of the cellular handling of sodium and potassium. An increased leak of sodium across the cell membrane as well as reduced activity of the sodium-potassium pump have been described both in hypertension[24 25] and in diabetes mellitus.[26 27] Disturbed sodium transport across the cell membrane has also been associated with hyperlipidaemia.[28] A defect in cellular regulation because of altered intracellular concentrations of essential cations might thus cause the cardiovascular risk factors. Genetic predisposition as well as environmental factors might determine which risk factors develop. Different environmental factors and factors of lifestyle, such as sedentary living and consumption of excess alcohol, salt, or saturated fat, might all have a role in the pathogenesis of the syndrome, and an aggregation of external factors could produce an aggregation of independent metabolic effects.

Another putative connecting link in the syndrome is disturbed calcium metabolism. In our study positive relations between serum calcium concentration (adjusted for albumin) and blood pressure, serum glucose concentration, and serum cholesterol concentration were seen independent of age, sex, obesity, and kidney function. An altered calcium balance with high serum calcium, serum parathyroid hormone, and urinary calcium concentrations and low concentrations of ionised calcium has been described in hypertensive subjects.[2 29-32] Total serum calcium concentration has been found to be positively related to blood pressure in population studies.[19 33] On the other hand, plasma ionised calcium concentration was negatively related to blood pressure in a population survey.[34] Altered plasma binding of calcium in subjects with hypertension might explain these divergent findings.[32] A raised intracellular calcium concentration has been found in these subjects,[35] and decreased calcium adenosine triphosphatase activity has been described in both subjects with hypertension[36] and those with diabetes mellitus.[37]

The findings of this study suggest that alterations of calcium concentration, within the physiological ranges, could play an important part in the development of the metabolic syndrome.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