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Serum calcium level: an independent risk factor for Cardio-vascular disease

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Abstract- 200 patients were studied during January 2013 to December 2014. Complete history, total serum calcium levels, lipid profile were measured to evaluate patient. 121 were males and 79 were females the ages of 45 and 65 years. We used linear regression model. Our variable were age, calcium, body mass index, cholesterol, HDL cholesterol, triglycerides and covariate were systolic and diastolic blood pressure, and pulse. Serum calcium was associated with systolic and diastolic blood pressure, serum cholesterol, serum triglyceride and HDL cholesterol in both sexes (P<0.001). Serum calcium levels were higher in men with a history of myocardial infarction than in those without in all age group (P<0.0001). Serum calcium level was independent risk factor for Myocardial Infarction when all the other variables were also included (P<0.0001).

Index Terms- Calcium, Serum Cholesterol, Serum triglyceride, Myocardial Infarction

I. Introduction

High systolic and diastolic blood pressure (BP) is associated with increased level of Serum Calcium level.[1] [2] it has been observed that in patients with hyperparathyroidism with high calcium level develop hypertension[3] and have an increased mortality rate due to cardiovascular diseases.[4] High level of serum calcium is also found to be correlated with high serum cholesterol and blood **glucose level[2] and therefore is apparently associated with the metabolic syndrome. Recently,** serum calcium has been reported to be an independent risk factor for myocardial infarction in middle-aged person.[5]

II. Methods

We studied 200 patient (121 males and 79 females) at Sri Mahant Indiresh Hospital of Sri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun from January 2014 to December 2014. This hospital is tertiary care hospital and cater mainly Garhwal region (Hills of northen India).

Clinical examination of every patient was done. BP and heart rate were noted.[6] Blood samples were taken in fasting state, and cholesterol, HDL cholesterol, and triglycerides were measured.[6] The reference range for cholesterol in our laboratory is < 200 mg/dL. The reference range for HDL cholesterol is 40 to 60 mg/dL; the range for triglycerides is <150mg/dL. Serum calcium was measured on Fusion-Johnson and Johnson equipment with reagents from Johnson and Johnson (reference range, 8.4 to 10.2 mg/100).

III. Statistical Analyses

Differences between age and serum calcium groups were evaluated with ANOVA. Linear trend was evaluated with linear regression. Linear association was evaluated by Pearson correlation coefficients. A sex-specific multiple linear regression model was used to control for confounding factors and included age, calcium, body mass index (BMI), cholesterol, HDL cholesterol, triglycerides, systolic BP, diastolic BP, and pulse as potential predictors. The regression coefficient is given as the standardized β coefficient. The data presented are mean±SD. Statistical analyses were performed with SPSS version 8.0 (SPSS Inc).

IV. Results

Subjects

The total number of subjects examined was 121 men (60.5%) and 79 women (39.5%). . The exclusion of patients with heart disease, stroke, or diabetes, pregnant women, and patients taking antihypertensive drugs had no effect on any of the results presented. Therefore, all subjects examined were included in the analyses.

There was a significant decrease in men and a significant increase in women in serum calcium with age (P<0.001)

Table 1. Characteristics of Male population:

Age Group, y	No.	Serum Calcium, mg/dL	Systolic BP, mm Hg	Diastolic BP, mm Hg	Serum Cholesterol, mg/dL	Serum HDL Cholesterol, mg/dL	Serum Triglycerides, mg/dL	BMI
45–49	12	8.5±0.10	130.6 ±8.4	85±6.3	210.14±7.01	42±7.63	130 ±11.13	24.6±0.4
50–54	34	8.6±0.20	138.8 ±11.4	89.6±9.4	220±11.10	40±0.31	145 ±9.23	25.6±0.3
55-59	38	9.6±.30	149.9 ±13.3	97.9±10.4	276±11.0	40±14	198±20	25.9±0.5
50–59	38	9.9±0.29	150.8 ±16.8	100.6±11.0	289±11.17	40±9	200 ±11.19	26.6±0.4
60–65	13	10.0±0.10	163.1 ±20.9	103.3±12.0	298±11.15	41±0.40	208 ±10.00	26.9±0.3
P(equality)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
P (linear trend)	<0.001	<0.001	<0.001	<0.001	<0.05	NS	NS	

Table 2. Characteristics of Female population:

Age Group, y	No.	Serum Calcium, mg/dL	Systolic BP, mm Hg	Diastolic BP, mm Hg	Serum Cholesterol, mg/dL	Serum HDL Cholesterol, mg/dL	Serum Triglycerides, mg/dL	BMI
45–49	13	8.86±0.30	126.7 ±10.5	76.0±8.6	204±9.0	41±2.39	134.16 ±4.72	22.5±4.7
50–54	27	8.98±0.10	137.3 ±11.2	88.3±9.3	210±10.0	42±2.33	138±3.98	23.5±2.7
55–59	26	9.00±0.10	141.6 ±14.5	97.6±10.3	220±11	1.66±0.39	148±4.74	25.4±4.8
60–65	13	9.29±0.11	151.6 ±19.1	107.6±11.8	6.67±1.26	1.70±0.43	158±5.09	26.7±5.4
P(equality)		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
P (linear trend)		<0.001	<0.001	<0.001	<0.001	NS	<0.001	<0.001

Serum Calcium and BP

There was a significant linear relation between serum calcium and BP in both men and women (correlation coefficients of 0.059 and 0.206 for systolic BP in the 2 genders and of 0.062 and 0.198 for diastolic BP, respectively; $P<0.001$). Because BP is strongly dependent on age, an age-stratified analysis was performed. The relation was found to be present within each age group and was similar in men and women (Figures 1 and 2). The association was still highly significant ($P<0.001$) after adjustment for all the other variables included in the multiple linear regression model.

Serum Calcium and Cholesterol

Cholesterol levels increased with increasing calcium levels in both men and women (Pearson correlation coefficients of 0.149 and 0.265, respectively; $P<0.001$) which was similar to that observed for BP. This significance remained after adjustment for all the other variables included in the model.

Serum Calcium and HDL Cholesterol

In both men and women, a significant ($P<0.001$) association existed between serum calcium and HDL cholesterol (Pearson correlation coefficients of 0.060 and 0.041, respectively) which remained after adjustment for other variables. However, the association appeared weaker than that between cholesterol and calcium.

Serum Calcium and Triglycerides

In both men and women, there was a significant linear correlation between serum calcium and triglycerides (correlation coefficients of 0.075 and 0.115, respectively<0.001). In men, this association remained significant after adjustment for the other variables, whereas in women, this correlation was no longer significant after adjustment for cholesterol.

Serum Calcium and Cardiovascular Diseases

Within each age group, both men and women with a history of myocardial infarction had higher serum calcium levels than

those without infarction. When linear regression with age as a covariant was used, this difference was significant (P<0.0001) in men but not in women. Similarly, with a logistic regression model that included the same variables as in the multiple linear regression analysis, serum calcium was statistically significant as an independent predictor of myocardial infarction in men (estimated odds ratio=0.1503, P<0.0001) but not in women (odds ratio=0.4812, P=NS). Similar to that observed for myocardial infarction, the serum calcium levels in men with angina pectoris were higher within each age group. This difference was statistically significant (P=0.024) in the age-adjusted linear regression model described above but not in the logistic regression model. In women, a similar but non-significant trend was observed. No significant difference was found in serum calcium levels in regard to patients with a history of stroke.

V. Discussion

In the present study, serum calcium was affected by age in both genders, with a gradual decrease with age in men and an increase in calcium at the time of menopause in women. This age-related pattern is similar to that described in other epidemiological studies.[1] [7]

We found a highly significant association between serum calcium and both systolic and diastolic BP in both genders, an association that persisted after adjustment for all the other variables in the linear regression model. When the importance of calcium in all aspects of physiology is considered, together with the huge amount of research done on hypertension, there are remarkably few studies on the relation between total serum calcium levels and BP. However, in the few available studies, [12] [8] the results are similar to those presented in this study. Calcium exists in 3 major forms in plasma. Approximately 50% is in the free or ionized form, which is the physiologically important fraction, 40% is bound to albumin, and the remaining 10% is in soluble complexes with anions such as bicarbonate, phosphate, and lactate.[9] Thus, total serum calcium will not only reflect calcium physiology but also be a function of the serum albumin level. Numerous algorithms have therefore been derived to correct for this effect,[10] but unfortunately, serum albumin data are not included in our study. This could be of considerable importance because in a report by Hu et al,[11] serum albumin also showed a consistent and strong association with systolic and diastolic BP.

In other epidemiological studies on calcium and BP, some investigators have corrected for serum albumin concentration. Thus, in the study by Kesteloot and Geboers[1] of 9321 men in the Belgian army, serum calcium values were not corrected, whereas in the study from Sweden by Lind et al,[2] which included >18 000 men and women, values were corrected and the association was still present and highly significant. On the other hand, in the British Regional Heart Study of 7735 healthy middle-aged men, Phillips and Shaper[8] found that the small but significant association between serum calcium and BP diminished after they corrected for serum albumin and became nonsignificant after they included serum globulins and hematocrit in the model.

There are several reports that ionized serum calcium actually is lower in hypertensive patients than in normal controls.[12] [13] To reconcile this with our findings, because there is a strong correlation between total and ionized serum calcium, one would have to assume that the binding characteristics for calcium and its carrier proteins are abnormal in hypertension. This has been found in a study of 28 hypertensive subjects compared with normotensive controls,[14] but until this finding is confirmed in other studies, it must be considered highly speculative.

To make the matter even more complicated, there seems to be a negative association between the intake of dietary calcium and BP,[15] and the serum calcium level has been reported to increase with calcium intake.[16] To settle these questions, large studies, which consider all of these variables, are needed.

In regards to serum calcium and lipids, there was a particularly strong association with cholesterol in both genders even after correction for age, BMI, and other possible risk factors. Thus, the standardized regression coefficient β for calcium, with cholesterol as dependent variable, was second only to age and the other lipids in the model. Serum calcium was also found to be an independent, significant predictor of the HDL cholesterol level, but the standardized regression coefficient was only half that seen for total cholesterol. In contrast, the association between serum calcium and triglycerides was weaker and disappeared in women, but not in men, in the linear regression analysis.

To the best of our knowledge, the relation between serum calcium and triglycerides has not been previously reported, whereas similar results regarding cholesterol were found by Lind et al.[2] As with hypertension, our results are confounded by the lack of correction for serum albumin, which has been reported to be positively correlated with serum cholesterol.[17] However, the similarity of the results in our study with the study by Lind et al,[2] in which they corrected for serum albumin, makes it unlikely that serum albumin had a major influence.

Our findings on BP and lipids are in agreement with findings in chronic hypercalcemia. Thus, hypertension[18] and hyperlipidemia[19] are common in patients with hyperparathyroidism, and these patients also have an increased mortality rate from cardiovascular diseases.[4] Moreover, serum calcium levels are higher in non–insulin-dependent diabetes mellitus[20] and are also positively associated with blood glucose in the general population.[2] An association between serum calcium and the metabolic syndrome has therefore been suggested.[2]

If such an association exists, one would expect serum calcium to be related to cardiovascular mortality and morbidity. Indeed, this has been demonstrated prospectively for myocardial infarction in a study in which serum calcium appeared as an independent risk factor in middle-aged men followed for 18 years.[5]Furthermore, in a study by Leifsson and Ahrén[21] that followed 22 000 men for a mean period of 10 years, the risk of premature death in men <50 years of age increased when serum calcium levels rose, even if the increase was within the normal range. As in hyperparathyroidism, this increase was mainly due to cardiovascular diseases.

With our data, we can thus far only perform a retrospective analysis on serum calcium in relation to cardiovascular diseases. In the questionnaire completed by the patients, questions on myocardial infarction, angina pectoris, and stroke were included. Not surprisingly, serum calcium levels were higher in those with

infarction and angina, but significantly so only for men with myocardial infarction when analyzed with logistic regression. In this respect, serum albumin is probably not a confounding factor, because serum albumin is found to be inversely related to cardiovascular diseases.[22] However, a positive association is no proof of causative relation. In the case of calcium and hypertension, one should be especially careful because there is an apparent discrepancy between results obtained with ionized and total serum calcium levels.

In men, BP increased with age whereas calcium decreased with age. Accordingly, BP must be influenced by other factors that in this respect are more important than calcium. It must also be recognized that serum calcium could merely be a marker for other factors of greater importance for hypertension and cardiovascular diseases. Thus, in the study by Resnick et al,[13] subjects with hypertension and high plasma renin activity also had elevated serum ionized calcium levels, and Alderman et al[23] reported that a 2 unit increase in plasma renin activity increased the overall incidence of myocardial infarction by 25%. Furthermore, the calcium-regulating hormones calcitonin, calcitriol, and parathyroid hormone have been related to hypertension, partly in association with plasma renin activity.[24] Finally, there may be interactions between serum calcium, phosphate, and magnesium,[13 25 26] as well as between calcium and sodium.

Our results are average values of large groups of individuals, and effects in subgroups may not be seen, as shown in the study by Hunt et al.[27] Thus, in their study on 875 subjects, no correlation between plasma ionized calcium and BP was found. However, after the older subjects were divided into tertiles on the basis of renin activity, there was a significant inverse correlation between ionized calcium and BP in the low renin group and a significant positive relation with systolic BP in the high renin group.

In addition to relations between serum calcium and cardiovascular risk factors, certain other observations should be noted. Despite a highly significant correlation between systolic and diastolic BP (correlation coefficient in men of 0.681), in men there was a negative association between cholesterol and systolic BP and a positive correlation between cholesterol and diastolic BP. For systolic BP, this is contrary to that reported by others.[28 29] However, as shown in Table 1⇫, there was an increase in systolic BP up to the age of 90 years, whereas diastolic BP and serum cholesterol peaked in those in their 60s and thereafter showed a decline. Because the age of our study population was high, this age-related pattern may explain the discrepancy with previous reports.

Furthermore, there was a significant correlation between pulse rate and BP in both genders. Because a highly significant relation between heart rate and the calcium/phosphate ratio has been described,[26] this could have an effect on the relation between calcium and BP. However, when pulse rate was excluded from the multiple linear regression analysis, this increased the corresponding standardized β coefficient in both genders by only 7%.

In conclusion, total serum calcium is strongly related to BP and serum lipids. This relation might be explained in part by covariation with serum albumin and may also be due to the association between serum calcium and other substances related to hypertension and heart disease. Regardless of this, however, total serum calcium appears to be a marker of cardiovascular disease, at least in men.

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