Relationship between calcitrophic hormones and blood pressure in elderly subjects

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The relationship between calcitrophic hormones and blood pressure has been investigated in 583 elderly subjects who were untreated for hypertension. Univariate analysis demonstrated that serum parathyroid hormone, calcitriol, albumin and calcium were correlated significantly with mean blood pressure (r = +0.15, +0.10, +0.14 and +0.11, respectively), as were body mass index and age (r = +0.19 and +0.10, respectively). Parathyroid hormone also was correlated positively with both age and calcitriol (r = +0.34 and +0.15, respectively) and negatively with plasma calcium and albumin (r = −0.09 and −0.09, respectively). Multivariate analysis demonstrated that when allowing for age and body mass index, parathyroid hormone and calcitriol were both significant independent determinants of the mean blood pressure. When other independent variables were included in the analysis, parathyroid hormone but not calcitriol remained a significant predictor of mean blood pressure. This study has demonstrated a weak but significant relationship between blood pressure and calcitrophic hormones in a group of elderly people. The data are consistent with the hypothesis that hypertension may be due in part to calcium deficiency.

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Alterations in calcium homeostasis may contribute to the pathogenesis of essential hypertension (1). Evidence to support this hypothesis has come from two particular lines of research. The first has involved studies of the abnormalities of intracellular calcium in platelets and their relationship to blood pressure (2). The second line of research has been to examine the effects of dietary calcium manipulation on blood pressure levels (3). In recent years attention has shifted to the possible role of calcitrophic hormones in the pathogenesis of hypertension. Several reports have documented that both animal and human hypertension is accompanied by alterations in levels of parathyroid hormone (PTH), calcitriol and calcitonin (4–6).

It is not clear from these studies whether high levels of PTH and calcitriol are a primary or secondary event. One recent study has suggested that calcitrophic hormones participate directly in the hypertensive process (5). These changes in hormone secretion might arise through a deficiency of dietary calcium, reduced intestinal absorption or increased urinary calcium excretion, which has been described previously in hypertension (7). An alternative possibility is that there may be a relationship between the age-related changes in blood pressure and age-related changes in mineral metabolism, such as increased secretion of PTH (8, 9).

We have had the opportunity to study a large group of elderly people who were not receiving any hypertensive therapy. We have used this group of subjects to test the hypothesis that increasing blood pressure is associated with increased levels of PTH and calcitriol.

Methods

Subjects

Busselton is a rural town in the southwest of Western Australia that has participated in regular epidemiological studies since 1966. In the 1987 survey, 61% of the population over 65 years of age attended a morning clinic after an overnight fast, completed a medical questionnaire, had measurements of blood pressure taken and provided fasting blood samples. This study reports results from 297 male and 286 female subjects who were not on any antihypertensive medication. Subjects who had a plasma creatinine level of more than 3SD above the population mean (≤127 µmol/l) were excluded from the study.

Single measurements of diastolic and systolic blood pressure were obtained in the supine position using a standard mercury sphygmomanometer after 5 min of rest. Diastolic blood pressure was taken as the disappearance of all sounds. Mean blood pressure
(MBP) was calculated as diastolic blood pressure plus one-third of the difference between systolic and diastolic blood pressure. Plasma creatinine, calcium and phosphate were measured by a SMAC II Analyst (Bayer Diagnostics, Tarrytown, NY). Calcitrophic hormones were measured on samples that had been frozen within 2 h of collection and remained frozen at −70°C until analysis in 1991. Intact PTH was measured by an immunochemiluminometric assay (10) that recognizes only the intact PTH molecule with an intra- and interassay variation at 8.0 pmol/l of 3.6% and 6.2%, respectively. Serum calcitriol levels were determined by a bovine thymus cytoceptor assay after initial extraction and purification of the sample (11); the intra- and interassay variations for this assay were 19% and 21%, respectively, at a level of 85 pmol/l. Body mass index (BMI) was calculated as height in metres divided by weight in kilograms squared. The albumin-adjusted calcium level was calculated from the formula: Adjusted calcium = Total calcium − ([Albumin − 40] × 0.02). We have shown previously that albumin-adjusted calcium when calculated in this way is correlated highly with dialysable calcium (12).

Analysis of the data was carried out in conjunction with a database containing the epidemiological data, which included age, BMI and blood pressure measurements. Statistical and data analysis were performed using the Statistical Package for Social Science. Relationships between the variables were assessed by simple correlation or by multiple stepwise regression analysis where the following independent variables were tested: age, BMI, PTH, calcitriol, albumin, calcium and phosphate. Only multiple correlations significant at \( p < 0.05 \) in a two-tailed test are reported.

Results

The mean values of various demographic and biochemical variables are shown in Table 1. Univariate correlates of MBP are shown in Table 2. Both age and BMI were correlated significantly with MBP, as were plasma albumin, calcium, PTH and calcitriol (Fig. 1), but not creatinine. Plasma phosphate was correlated inversely with MBP. The relationship between MBP and calcium was abolished when the calcium concentration was adjusted for albumin.

Parathyroid hormone was correlated positively with calcitriol and age, whereas it was correlated inversely with plasma albumin and calcium but not with albumin-adjusted calcium (Table 3). Calcitriol was correlated inversely with creatinine and positively with plasma albumin and calcium, but not with age (Table 3).

To explore further the interrelationships between the various predictors of blood pressure, we carried out multiple regression analyses with MBP as the dependent variable and other measured variables as independent variables (Table 4). Initially we used all measured variables that were correlated with MBP by simple linear correlation analysis, as shown in Table 2. This analysis showed that, having allowed for age and BMI, which are two accepted correlates of blood pressure (13, 14), PTH but not calcitriol was still an important independent predictor of blood pressure (Table 4a).

Then we used multiple regression analyses to examine the hypothesis that calcitrophic hormones were important independent predictors of MBP by examining MBP as a dependent variable with age, BMI, PTH and calcitriol as independent predictors. Under these circumstances age was replaced by calcitriol in the regression equation (Table 4b). Analysis of the male and female data separately did not substantially alter these conclusions.

Discussion

This study was carried out in order to see whether there was any relationship between levels of calcitrophic hormones and blood pressure in a group of elderly people who were not receiving any hypertensive medication at the time of study. We believe that this is the largest group of people in whom this relationship

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<th>Table 1. Mean values for demographic and biochemical variables.</th>
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<td>Mean age (years)</td>
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<td>Mean blood pressure (mmHg)</td>
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<td>Body mass index (kg/m²)</td>
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<th>Table 2. Simple regression analyses of mean blood pressure with various demographic and biochemical variables.</th>
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<td>Mean blood pressure</td>
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<td>Age (years)</td>
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\( r \): correlation coefficient; \( \beta \): regression coefficient; \( p \): two-tailed probability.
has been investigated and described in the literature. Using a within-group analysis we found a positive relationship between MBP and PTH, which remained significant after the effects of confounding variables such as BMI and age were taken into account by multiple regression analysis. These findings are constant with those of Young et al. (4), who found a similar relationship in a combined group of normotensive and hypertensive men. Hvarfner et al. (6) also found a positive relationship between PTH and blood pressure in hypertensive subjects, but this relationship disappeared when the analysis included normotensive people. Studies of healthy subjects alone have revealed conflicting findings with data in favour of a significant relationship (15), while another study of a similar group failed to demonstrate a correlation between PTH and either systolic or diastolic blood pressure (16).

The relationship between MBP and PTH, although weak, was similar to the relationship between age, BMI and MBP (age and BMI both being accepted correlates of MBP). Furthermore, the relationship between MBP and PTH was not as strong as those described in other studies (4, 15). One reason for this may be that because our group included subjects who were not on any hypertensive medication, it did not include people with significant hypertension. Possibly the most important factor that may contribute to the relative weakness of the relationship between PTH and blood pressure is that there are other determinants of blood pressure apart from calcitrophic hormones. In particular, Resnick et al. (17) has drawn attention to elevated levels of calcitrophic hormones in a group of hypertensive patients who have salt sensitivity and low renin levels. Thus, it is possible that only some of our subjects were within this low renin category, thus contributing to the weaker relationship.

Our findings also demonstrated that calcitriol was a significant determinant of MBP when age and BMI were allowed for, but this relationship was attenuated when other biochemical determinants were included in the multiple regression analysis. In particular, the correlation of albumin and calcitriol may have excluded calcitriol from the multiple regression equation. The correlation of these two variables is unexplained; however, other workers have noted a relationship between blood pressure and albumin (6). The findings

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& \text{r} & \beta & \text{p} & \text{r} & \beta & \text{p} \\
\hline
\text{Age (years)} & +0.335 & 0.082 & 0.001 & - & - & - \\
\text{Serum calcitriol (pmol/l)} & +0.148 & 0.007 & 0.002 & - & - & - \\
\text{Plasma albumin (g/l)} & -0.085 & -0.051 & 0.040 & +0.131 & 1.518 & 0.002 \\
\text{Plasma calcium (µmol/l)} & -0.091 & -1.520 & 0.028 & +0.122 & 39.13 & 0.006 \\
\text{Plasma creatinine (µmol/l)} & - & - & - & -0.192 & -0.325 & 0.002 \\
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*r: correlation coefficient; \(\beta\): regression coefficient; p: two-tailed probability (only those values significant at \(p < 0.05\) are shown).
in this study support those of two other studies, which demonstrated an increase in blood pressure after calcitriol administration (17, 18). However, two other studies of normotensive and hypertensive patients with impaired glucose tolerance demonstrated reductions in blood pressure following alphacalcidol therapy (19, 20). The reasons for these contrasting findings could not be ascribed to the glucose intolerance of these patients, but as with PTH the response to vitamin D therapy may be dependent upon sodium and renin levels.

Increased levels of PTH in subjects with high blood pressure may be due to a urinary calcium leak which lowers plasma calcium levels and causes a compensatory increase in PTH (7). The findings from our study are in accordance with this hypothesis to the extent that PTH and MBP were correlated positively with each other. In addition, PTH and calcitriol levels were correlated positively with each other. We have found previously that both PTH and calcitriol levels rise after dietary calcium deprivation in healthy pre- and postmenopausal women (21, 22) and in subjects with mild to moderate chronic renal failure (23). Consequently, it is possible that within our population there were subjects who were not taking sufficient dietary calcium to compensate for urinary loss and therefore developed a relative increase in calcitropic hormones and blood pressure. It is possible also that vitamin D deficiency may have resulted in a rise in PTH, but under those circumstances calcitriol would not be expected to be elevated.

Thus, our study strengthens other epidemiological data suggesting a relationship between relative calcium deficiency and raised blood pressure. Much of the evidence supporting the calcium deficiency hypothesis has come from studies of the effect of calcium supplementation on blood pressure (24–26), including a recent study that describes a reduced incidence of hypertensive disorders of pregnancy in women receiving calcium supplementation (27). However, the hypothesis remains contentious because several studies have failed to show any effect of such supplementation (28–30).

Once again, subtle differences in salt balance or renin status may determine the response or non-response to calcium supplementation (5).

In summary, we have demonstrated a relationship between calcitropic hormones and MBP in a large group of elderly people. This relationship is consistent with the concept of a relative calcium deficiency that potentially may play an aetiological role in the rise of blood pressure in elderly subjects.

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References


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