Alterations in Calcium Metabolism in Young People at Risk for Primary Hypertension

The Dutch Hypertension and Offspring Study

Ingrid M.S. van Hooft, Diederick E. Grobbee, Marijke Frolich, Huibert A.P. Pols, and Albert Hofman

Several disturbances in calcium metabolism have been reported in primary hypertensive subjects. It is, however, not clear whether these alterations predate the development of hypertension or occur as a consequence of high blood pressure. We studied indexes of calcium metabolism in three groups of normotensive children with different familial predispositions for hypertension, based on parental blood pressure levels, with two, one, or no hypertensive parents. Plasma intact parathyroid hormone [1–84] was higher in the offspring of hypertensive parents compared with offspring of normotensive parents (difference, 0.58 pmol/L; standard error of the difference [SED], 0.24; p=0.02). Mean serum calcium levels were slightly reduced in the offspring of two hypertensive parents (−0.019 mmol/L; SED=0.013, p=0.17). Plasma magnesium and phosphate levels were lower in the offspring of hypertensive parents (−0.032 mmol/L [SED=0.016, p=0.05] and −0.045 mmol/L [SED=0.024, p=0.05], respectively). Mean 1,25-dihydroxyvitamin D3 levels were similar among the groups. No differences in dietary intake of calcium, phosphate, or fiber were found. Urinary calcium excretion per 24 hours and the ratio of 24-hour urinary calcium excretion to daily calcium intake were somewhat higher in the offspring of hypertensive parents. Renal fractional excretion of calcium was similar in the offspring of two hypertensive parents, and renal fractional excretion of phosphate was lower in the offspring of two hypertensive parents compared with offspring of two normotensive parents (−1.50%, SED=0.74, p=0.05). These findings indicate that changes in calcium metabolism may be implicated in the early pathogenesis of primary hypertension and suggest a reduced renal sensitivity to parathyroid hormone in those at risk for hypertension. (Hypertension 1993;21:267–272)

KEY WORDS • calcium • hypertension, primary • family characteristics • parathyroid hormones

Several disturbances of calcium metabolism have been associated with hypertension. It has been suggested that a low dietary calcium intake increases the risk for high blood pressure. In addition, some hypertensive subjects appear to have lower serum ionized calcium levels, increased urinary excretion of calcium, raised intracellular calcium levels, and reduced cellular membrane calcium binding. Changes in magnesium and phosphate metabolism may be implicated in the relation between calcium and blood pressure regulation. In some hypertensive subjects, urinary excretion of magnesium may be decreased and show an inverse relation with blood pressure. Serum phosphate concentration is reported to be lower in hypertension and negatively related to blood pressure. Besides changes in serum and urinary electrolytes, raised circulating parathyroid hormone (PTH) levels have been demonstrated in hypertensive individuals. We reported previously that plasma intact PTH is raised in young hypertensive subjects compared with normotensive subjects of similar age, suggesting that alterations in calcium metabolism may be implicated in the early pathogenesis of primary hypertension. Discussion remains as to whether changes in calcium metabolism are causally related to the development of high blood pressure. In genetically hypertensive rats, calcium supplementation during the developmental phase of hypertension diminished the blood pressure increase. In another study, however, genetically hypertensive rats fed a calcium-deficient diet did not show an increased blood pressure rise compared with rats fed a normal diet. Parathyroidectomy in young genetically hypertensive rats, while keeping a normal serum calcium level, delayed the rise in systolic blood pressure for 42 weeks. In humans, information on the part played by changes in calcium metabolism in the development of high blood pressure may be gained from comparison of...
parameters of calcium homeostasis between offspring of hypertensive parents and offspring of normotensive parents.25 We studied indexes of calcium metabolism in 180 normotensive offspring from 121 families with two, one, or no hypertensive parents, who were recruited out of 1,642 couples participating in a Dutch population study of risk factors for cardiovascular disease.

Methods

Population

The Dutch Hypertension and Offspring Study is a collaborative study of four Dutch Universities and is conducted in the town of Zoetermeer, a suburban residential area near The Hague in The Netherlands.26 From 1975 to 1979, all residents of two districts of Zoetermeer were invited to participate in a study of blood pressure and other cardiovascular risk indicators (EPOZ study).27 Blood pressure was measured in 10,532 (78%) of 13,462 eligible subjects. This group included 1,642 parental couples. A stringent selection procedure was applied to these couples to select groups of offspring with a maximal contrast in familial predisposition for hypertension. The procedures for selection have been described elsewhere.26 In brief, individual parents with both systolic blood pressure and diastolic blood pressure in the upper (“hypertensive”) or lower (“normotensive”) quartile of the age- and sex-specific blood pressure distribution were selected. Those taking antihypertensive medication were included in the hypertensive group. Couples of two hypertensive parents, of one hypertensive and one normotensive parent, and of two normotensive parents were invited for remeasurement of blood pressure in 1986. On this occasion, the same criteria for hypertension and normotension were applied as for the initial screening. Of 250 parental couples that were remeasured (80% of those invited), 51 couples of 74 remained in the group of two hypertensive parents, 35 of 106 in the group of one hypertensive and one normotensive parent, and 35 of 70 in the group of two normotensive parents. Together, these 121 selected parental couples had 291 healthy biological children, aged between 5 and 30 years, who were invited to take part in this study. Of these, 180 offspring (62%) of 97 families gave informed consent and participated in the study: 69 children with two hypertensive parents, 58 children with one hypertensive and one normotensive parent, and 53 children with two normotensive parents.

Measurements

The groups of offspring visited the research center twice. In 1987, a short protocol was followed for anthropometric and blood pressure measurements, a blood sample was obtained for measurement of parameters of calcium metabolism, and a 24-hour urine sample was collected. In 1988, the measurements in the groups of offspring were repeated, this time including a 3-hour fasting period between 7 and 10 AM during which urine was sampled; a blood sample was taken after 90 minutes, at 8:30 AM. The participants had been asked to refrain from intake of food and beverages starting from midnight.

Blood pressure was measured on the left arm with a random-zero sphygmomanometer by a trained paramedical assistant. A series of two readings was made with the subject sitting, and the mean of these readings was used in the analysis. A fasting venous blood sample was obtained, and serum and plasma samples were stored at −70°C. All participants collected two 24-hour urine samples. Levels of serum total calcium, inorganic phosphate, and magnesium as well as urinary calcium, sodium, potassium, and creatinine were measured by standard laboratory methods. All variables were measured twice at each of the two visits, with the exception of plasma magnesium (first examination only) and 1,25-dihydroxyvitamin D₃ and clearance parameters (second examination only). Fractional excretion of electrolytes was calculated from the concentration in the 3-hour fasting urine portion (Uᵢ), with the concentration of plasma creatinine (P Cr), the urinary concentration of creatinine (U Cr), and the plasma concentration of the electrolyte (P X) according to the following formula: (Uᵢ • P X)/(U Cr • P Cr). At the second visit, dietary intake of calcium, phosphate, fiber, and total energy was assessed by a 1-month dietary recall with a cross check.28 Plasma intact PTH [1–84] was determined by a two-step immunnochemical method.19,29 1,25-Dihydroxyvitamin D₃ was measured by radioimmunoassay (Inctar Corp., Stillwater, Minn.). None of the participants used any medication or other substance known to influence calcium metabolism.

Data Analysis

Descriptive data for the three groups are presented as means and standard deviations. For comparison between groups, means and SEM are given, and the difference (with standard error of the difference [SED]) compared with the offspring of two normotensive parents is presented. Adjustments for differences in age, height, weight, and proportion of males between the three groups were made using a model for multiple linear regression. Adjusted values were used for comparisons between groups, and a two-sided t test was applied to assess statistical significance. If variables were measured twice, the mean of two measurements is given.

Associations between study variables (blood, urinary, and dietary variables related to calcium metabolism) were studied across groups and adjusted for group status (using indicator variables) and age, height, weight, and gender by multiple regression analysis. Regression coefficients are given with SEM.

Results

General Characteristics

Blood pressure, age, and anthropometric characteristics of the participating parental couples and their offspring in 1987 are given in Table 1. The selection based on age- and gender-specific blood pressure percentiles resulted in marked differences in parental blood pressure between the groups even though a small proportion of parents were taking drug therapy for hypertension. None of the children and young adults had clear hypertension, but blood pressure levels were higher in offspring of two hypertensive parents compared with offspring of two normotensive parents. No differences in 24-hour sodium and potassium urinary excretion were present between the groups of offspring.
Parameters of Calcium Metabolism

The mean levels of serum electrolytes, plasma intact PTH [1–84], and 1,25-dihydroxyvitamin D$_3$ are given in Table 2. Serum total calcium was slightly but not significantly lower in the offspring of two hypertensive parents compared with offspring of two normotensive parents. Serum magnesium and serum phosphate levels were reduced in the offspring of hypertensive parents: −0.032 mmol/L (SED=0.016, p=0.05) and −0.045 mmol/L (SED=0.024, p=0.05), respectively. Plasma intact PTH [1–84] was significantly higher both in the offspring of two hypertensive parents and in the offspring of one hypertensive parent compared with offspring of two normotensive parents. No differences were seen for the plasma level of 1,25-dihydroxyvitamin D$_3$ between the groups.

Daily dietary intake of nutrients important for calcium metabolism are given in Table 3. No statistically significant differences between the groups were seen for both total or energy-adjusted dietary intake of calcium, phosphate, or fiber.

The 24-hour urinary calcium excretion was somewhat higher, but not significantly so, in the offspring of hypertensive parents (Table 4). Twenty-four-hour urinary excretion of phosphate and creatinine were similar among the groups. During the 3-hour fasting period, the absolute excretion of calcium and phosphate per hour was similar among the three groups. Also, fractional excretion was the same for calcium, but fractional phosphate excretion was significantly lower in the offspring of two hypertensive parents (Table 4). The ratio of 24-hour urinary calcium excretion to daily dietary calcium intake was somewhat higher in the offspring of two hypertensive parents. Twenty-four-hour sodium excretion was similar in the groups (Table 1). The ratio of the 24-hour urinary excretion of calcium to sodium appeared to be somewhat higher in the offspring of two hypertensive parents compared with the offspring of two

<table>
<thead>
<tr>
<th>Index</th>
<th>Offspring of two normotensive parents</th>
<th>Offspring of one hypertensive parent</th>
<th>Offspring of two hypertensive parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mmol/L)*</td>
<td>2.36 (0.011)</td>
<td>2.37 (0.011)</td>
<td>2.34 (0.008)</td>
</tr>
<tr>
<td>Phosphate (mmol/L)*</td>
<td>1.18 (0.018)</td>
<td>1.14 (0.020)</td>
<td>1.13 (0.015)†</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.87 (0.013)</td>
<td>0.85 (0.011)</td>
<td>0.84 (0.011)†</td>
</tr>
<tr>
<td>Parathyroid hormone [1–84] (pmol/L)*</td>
<td>3.12 (0.187)</td>
<td>3.77 (0.106)†</td>
<td>3.70 (0.155)†</td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin D$_3$ (pmol/L)‡</td>
<td>68.1 (3.47)</td>
<td>...</td>
<td>67.4 (2.87)</td>
</tr>
</tbody>
</table>

Values are mean (±SEM), adjusted for differences in age, height, body weight, and gender.

*Values were calculated as the average of two examinations for each participant.

†p<0.05, for the difference with offspring of two normotensive parents.

‡Measured in offspring of two normotensive parents and of two hypertensive parents only.
TABLE 3. Total and Energy-Adjusted Dietary Intake of Calcium, Phosphate, and Fiber in Three Groups of Offspring

<table>
<thead>
<tr>
<th>Variables measured</th>
<th>Offspring of two normotensive parents</th>
<th>Offspring of one hypertensive parent</th>
<th>Offspring of two hypertensive parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,644 (92.1)</td>
<td>1,461 (86.1)</td>
<td>1,434 (76.9)</td>
</tr>
<tr>
<td>Energy adjusted</td>
<td>1,580 (75.2)</td>
<td>1,483 (71.1)</td>
<td>1,479 (63.9)</td>
</tr>
<tr>
<td>Phosphate (mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2,194 (94.9)</td>
<td>2,040 (88.7)</td>
<td>2,023 (79.2)</td>
</tr>
<tr>
<td>Energy adjusted</td>
<td>2,088 (61.1)</td>
<td>2,103 (57.8)</td>
<td>2,081 (51.9)</td>
</tr>
<tr>
<td>Fiber (g/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31.6 (1.40)</td>
<td>31.5 (1.34)</td>
<td>30.6 (1.20)</td>
</tr>
<tr>
<td>Energy adjusted</td>
<td>30.3 (1.23)</td>
<td>31.9 (1.16)</td>
<td>31.2 (1.04)</td>
</tr>
</tbody>
</table>

Values are mean (±SEM), adjusted for differences in age, height, body weight, and gender. Values in offspring of two hypertensive parents and offspring of one hypertensive parent did not show statistically significant differences with values in offspring of two normotensive parents.

Several relations between variables were studied across the groups. Plasma intact PTH [1–84] was inversely associated with serum calcium (−2.30 pmol/mmol, SEM = 1.15, p=0.05). 1,25-Dihydroxyvitamin D₃ tended to be positively associated with PTH [1–84], but this association failed to reach statistical significance (3.16 pmol/mmol, SEM = 1.88, NS). No relation between either plasma phosphate or plasma calcium with 1,25-dihydroxyvitamin D₃ was seen. A positive association for fractional excretion of phosphate and PTH [1–84] was observed of 0.56 %/(pmol/L) (SEM = 0.023, p = 0.01). No relations were seen for plasma intact PTH [1–84] either with dietary intake of calcium or phosphate or with the ratio of 24-hour excretion to dietary intake of calcium or phosphate. Twenty-four-hour sodium excretion was related to 24-hour calcium excretion (0.014 mmol/mmol, SEM = 0.003, p = 0.001) but not to plasma intact PTH [1–84].

To assess whether the differences in indexes of calcium metabolism had been confounded by the differences in blood pressure between the groups, we obtained values for levels of serum calcium, phosphate, magnesium, and plasma intact PTH [1–84] adjusted for blood pressure (Table 5).

**Discussion**

Our observation of slightly reduced serum calcium levels and significantly raised plasma intact PTH [1–84], combined with decreased serum magnesium and phosphate levels, in prehypertensive young subjects genetically at risk for hypertension supports the view that disturbances in calcium metabolism are present in the early phase of primary hypertension and may precede the development of high blood pressure.

Before this conclusion can be accepted, some issues need to be addressed. The offspring of hypertensive parents participating in the present study already had higher average blood pressure levels than the offspring of normotensive parents (Table 1). This is in agreement with observations in previous studies in young subjects.

TABLE 4. Twenty-four-Hour Urinary Excretion, Fasting Clearances, and Ratio of 24-Hour Urinary Excretion to Dietary Intake in Three Groups of Offspring

<table>
<thead>
<tr>
<th>Variables measured</th>
<th>Offspring of two normotensive parents</th>
<th>Offspring of one hypertensive parent</th>
<th>Offspring of two hypertensive parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour urinary excretion*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/24 hr)</td>
<td>3.10 (0.242)</td>
<td>3.48 (0.225)</td>
<td>3.48 (0.205)</td>
</tr>
<tr>
<td>Phosphate (mmol/24 hr)</td>
<td>32.5 (1.63)</td>
<td>32.3 (1.53)</td>
<td>31.2 (1.34)</td>
</tr>
<tr>
<td>Creatinine (mmol/24 hr)</td>
<td>13.7 (0.41)</td>
<td>13.2 (0.39)</td>
<td>13.4 (0.35)</td>
</tr>
<tr>
<td>Fasting clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/hr)</td>
<td>0.16 (0.011)</td>
<td>0.15 (0.010)</td>
<td>0.16 (0.009)</td>
</tr>
<tr>
<td>Phosphate (mmol/hr)</td>
<td>0.67 (0.011)</td>
<td>0.60 (0.051)</td>
<td>0.54 (0.047)</td>
</tr>
<tr>
<td>Fractional calcium excretion (%)</td>
<td>0.88 (0.057)</td>
<td>0.81 (0.052)</td>
<td>0.87 (0.047)</td>
</tr>
<tr>
<td>Fractional phosphate excretion (%)</td>
<td>7.84 (0.570)</td>
<td>7.04 (0.520)</td>
<td>6.34 (0.476)†</td>
</tr>
<tr>
<td>Ratio of 24-hour urinary excretion to dietary intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (%)</td>
<td>8.8 (1.01)</td>
<td>10.7 (0.95)</td>
<td>10.9 (0.84)</td>
</tr>
<tr>
<td>Phosphate (%)</td>
<td>48.3 (3.08)</td>
<td>52.0 (2.87)</td>
<td>49.2 (2.57)</td>
</tr>
</tbody>
</table>

Values are mean (±SEM), adjusted for differences in age, height, body weight, and gender.

*Values were calculated as the average of two examinations for each participant.

†p<0.05, for the difference with offspring of two normotensive parents.
with and without a family history of hypertension, and it probably reflects the inevitable expression of the large difference in genetic susceptibility. Although none of the children had clear hypertension, it is conceivable that the differences in blood pressure between the groups may have caused differences in calcium metabolism rather than the reverse. Although this possibility is difficult to exclude, one approach may be to adjust the observed differences for the difference in blood pressure between the groups (Table 5). Adjustment for differences in diastolic blood pressure did not clearly affect the level of and small differences in serum calcium between the groups, although the difference between the offspring of two hypertensive parents and the offspring of two normotensive parents just reached statistical significance. The difference for serum magnesium between the groups remained similar and statistically significant. After adjustments for diastolic blood pressure, the differences in plasma intact PTH [1–84] became smaller but remained statistically significant between the offspring of two hypertensive parents and the offspring of two normotensive parents. The difference in plasma phosphate became smaller and failed to reach statistical significance. It should be noted, however, that adjusting for blood pressure level may also obscure true differences in characteristics related to the development of high blood pressure, because offspring with the highest blood pressures may be those with the highest risk of future hypertension.

Differences in diet between the groups may be important in explaining our findings. Of particular interest are calcium intake and nutrients that may interfere with the intestinal absorption of calcium, notably, dietary fiber and phosphate. However, the levels of dietary calcium, phosphate, and fiber intake were not significantly different between the groups, and the small differences that were observed are unlikely to be fully responsible for the differences found in blood levels of calcium and intact PTH [1–84]. In agreement with this, when dietary factors were included in a multiple regression analysis, the differences between the groups for the various blood values of calcium metabolism remained similar.

1,25-Dihydroxyvitamin D₃, necessary for intestinal calcium absorption and bone resorption of calcium, may also affect calcium balance. The plasma level of 1,25-dihydroxyvitamin D₃ was not different between the groups and did not show a relation with either plasma phosphate, plasma calcium, or plasma intact PTH [1–84] levels.

Our findings of a relatively reduced serum calcium and increased plasma PTH [1–84] level in the offspring of hypertensive parents suggest a relative calcium deficiency in the offspring of hypertensive parents that is partly compensated by an increased plasma PTH. This profile of an increased plasma intact PTH [1–84] level and a somewhat lower serum calcium level in the offspring of hypertensive parents might be related to their risk for primary hypertension. PTH is known to increase intracellular calcium concentration and might thereby directly affect vascular smooth muscle tension. We previously observed that the decrease in diastolic blood pressure to calcium supplementation in offspring with relatively high blood pressure was most clear in subjects with a relatively high plasma PTH [1–84] or low serum calcium. In one other study, hypertensive subjects with a relatively large urinary calcium excretion showed more pronounced decreases in blood pressure to calcium supplementation compared with those with normal urinary calcium excretion. Calcium supplementation was reported to diminish the blood pressure increase and weight gain that accompany a high salt intake and is known to increase the urinary excretion of sodium.

Although differences in intestinal absorption and bone resorption of calcium between the groups of offspring at different risk for hypertension cannot be excluded, several of our findings suggest that the kidney may play a part in the calcium deficiency. An increased renal calcium excretion at a given level of calcium intake might result in a lower plasma calcium level. The relatively higher ratio of urinary calcium excretion to dietary calcium intake in the offspring of two hypertensive parents, together with the lower plasma calcium in this group, supports this possibility. However, the similar absolute and fractional calcium excretion in the 3-hour fasting morning period in the three groups is at variance. In a recent study by Young and coworkers (unpublished results), a difference in 24-hour urinary calcium excretion between hypertensive and normotensive subjects could be detected only with subjects on a controlled diet of either 400 or 1,400 mg calcium, and not with subjects on a liberal diet. Moreover, no differences in fasting urinary calcium excretion with subjects on either of the two diets could be shown between the hypertensive and normotensive subjects (Young et al, unpublished results). We suggest, therefore, that the small differences in our study in 24-hour urinary calcium excretion are obscured by the liberal calcium intake of the participants. The differences in urinary calcium excretion might be best studied relative to the

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<td>1.14 (0.015)</td>
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<tr>
<td>Magnesium (mmol/L)</td>
<td>0.88 (0.013)</td>
<td>0.85 (0.011)</td>
<td>0.84 (0.011)</td>
</tr>
<tr>
<td>Parathyroid hormone [1–84] (pmol/L)*</td>
<td>3.18 (0.173)</td>
<td>3.76 (0.174)†</td>
<td>3.66 (0.148)†</td>
</tr>
</tbody>
</table>

Values are mean (±SEM), adjusted for differences in age, height, body weight, gender, and diastolic blood pressure.
*Values were calculated as the average of two examinations for each participant.
†p<0.05, for the difference with offspring of two normotensive parents.
estimated daily calcium intake, as shown in Table 4. Plasma intact PTH [1–84] was inversely related to plasma calcium and was higher in the offspring of two hypertensive parents. Moreover, plasma intact PTH [1–84] was related to renal fractional excretion of both calcium and phosphate. Given these relations, one would expect to find a higher fractional excretion of phosphate and a lower fractional excretion of calcium in the offspring of hypertensive parents due to the higher plasma intact PTH [1–84] in this group, but the opposite was found. Apparently, the kidney in the offspring of hypertensive parents is less sensitive to PTH. Alternatively, the higher level of plasma intact PTH [1–84] in the offspring of hypertensive parents may be viewed as secondary to a relative calcium deficiency, which could arise from a renal calcium leak as proposed by McCarron et al.13 and Strazullo et al.14 In the context of a decreased renal sensitivity to intact PTH [1–84], the level of 1,25-dihydroxyvitamin D₃, activated by PTH in the kidney, can be regarded as inappropriately low in the offspring of hypertensive parents. More research on calcium metabolism in these groups of offspring is needed. In particular, oral and intravenous calcium challenges, to study possible differences in intestinal calcium absorption, and PTH stimulation tests of renal cyclic AMP production and urinary calcium and phosphate excretion are of interest.

In summary, it appears that calcium balance is maintained at a higher level of circulating PTH in offspring of hypertensive parents compared with offspring of normotensive parents, and this may be due to a decreased sensitivity of the kidney to PTH. Our findings suggest that certain alterations in calcium metabolism may play a part in the development of high blood pressure in young subjects genetically at risk for hypertension.

Acknowledgments

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References

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