ABSTRACT

Background: Intake of calcium from the diet is inversely associated with blood pressure in observational studies and animal models but randomized trials in humans have found only small effects of calcium supplementation on blood pressure. A blood pressure–lowering effect of calcium supplementation may thus be restricted to persons with a low intake of calcium from the diet and specific genetic or other characteristics.

Objective: A randomized trial was conducted to assess the effect of calcium supplementation on blood pressure in African American adolescents. Rapid growth during adolescence may increase calcium requirements, and avoidance of milk and milk products by some African Americans can result in low intake of calcium.

Design: One hundred sixteen adolescents (65 girls, 51 boys; mean age: 15.8 y) were given calcium (1.5 g/d) or placebo for 8 wk in a randomized, double-blind, crossover design. Blood pressure was measured after 2, 4, and 8 wk. Dietary calcium was determined with a validated food-frequency questionnaire.

Results: The net effect (±SE) of calcium supplementation on diastolic blood pressure was a reduction of 1.9 ± 1.1 mm Hg (P = 0.04, one-tailed t test). Blood pressure reduction was greater in adolescents with lower intake of calcium from the diet (P = 0.003, one-tailed t test for interaction): −4.9 ± 1.6, −2.3 ± 1.6, and 1.4 ± 1.8 mm Hg for change in the lower (0.024–0.067 g Ca/MJ), middle (0.069–0.091 g Ca/MJ), and upper (0.093–0.217 g Ca/MJ) tertiles, respectively. No main effect on systolic blood pressure was detected.


KEY WORDS Hypertension, blood pressure, calcium, diet, African Americans, adolescents

INTRODUCTION

The hypothesis that increased dietary intake of calcium can lead to a reduction in blood pressure stems from epidemiologic data and animal models. An inverse association between stroke mortality and water hardness led to the first suggestion of an antihypertensive effect of calcium carbonate (1–3). Subsequent epidemiologic studies across several countries and age groups presented a fairly consistent pattern of inverse associations between seated blood pressure and calcium intake from food (4–11). In the National Health and Nutrition Examination Survey (NHANES), this association was stronger in blacks than in whites (12). Three large prospective studies found protective relations between dietary intake of calcium and the incidence of hypertension (13–15), although this relation was limited to lean subjects in one cohort (13). There is also substantial evidence from the spontaneously hypertensive rat model that dietary calcium supplementation blunts the age-related rise in blood pressure that characterizes these animals (16–18).

However, consistent blood pressure–lowering effects of calcium supplementation in randomized trials have not been observed. A meta-analysis of trials in pregnant women found net blood pressure reductions in 10 of 12 trials (19). A preventive effect on the incidence of hypertension was observed in all 8 trials assessing this endpoint, and the magnitude of this protective effect was greatest in younger participants. Subsequently, a large multicenter preeclampsia prevention trial (n = 4589) found a small reduction of 10% (P = 0.05) in the incidence of hypertension in pregnant women but no significant decreases in blood pressure with 2 g Ca/d from calcium carbonate (20). This reduction in incidence is comparable with that found per gram of dietary calcium in the NHANES Epidemiologic Follow-up (15), but was much smaller than that expected from meta-analyses of previous trials.

Meta-analyses of trials in nonpregnant adults found evidence for only a small effect of calcium supplementation on blood pressure (21–26). This pattern of findings suggests that although the blood pressure–lowering effect of a diet rich in calcium may be substantial, the effect of calcium supplementation is small.

---

1From the Department of Preventive Medicine, Institute for Prevention Research and the Department of Pediatrics, Division of Pediatric Cardiology, University of Southern California School of Medicine, Los Angeles; and the Department of Health Systems Research, Louisiana State University School of Medicine in New Orleans.

2Supported by grant (R01HL42932) from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

3Address reprint requests to JH Dwyer, University of Southern California, Department of Preventive Medicine, 1540 Alcazar Street CHP 205, Los Angeles CA 90033-4500. E-mail: jimdwye@hsc.usc.edu.

Received July 28, 1997.

Accepted for publication April 23, 1998.
However, the effect may be greater in persons with calcium deficiency induced by increased requirements or low intake from the diet. In addition, there may be genetic heterogeneity in the systemic response to restricted calcium intake (27).

The current study was designed to assess a blood pressure-lowering effect of calcium supplementation in African American adolescents. African Americans were selected for study not only because they have a higher prevalence of hypertension than whites (28–31), but because several factors may converge to produce both increased calcium requirements and low dietary intakes of calcium. The rapid growth and hormonal changes associated with adolescence may affect calcium requirements in a manner analogous to pregnancy. The high prevalence of lactose intolerance, or apparent lactose intolerance (32), in African Americans (33) may contribute to a low intake of calcium from the diet. It was thus hypothesized that calcium supplementation would induce a lowering of blood pressure in this group and that the effect would be greatest in those subjects with a relatively low intake of calcium from their diet.

SUBJECTS AND METHODS

Subjects

Eligible subjects included all self-identified African American students enrolled in grades 10–12 at 3 high schools in a suburb of Los Angeles. In addition, subjects were screened for seated systolic blood pressure (SBP) > 115 mm Hg at 2 consecutive examinations separated by ≥1 d. Participants were enrolled only if they and their parent or guardian signed an informed consent form. The consent form and study procedures were approved by the Research Committee of the University of Southern California School of Medicine. Individuals were excluded from participation if they reported diabetes, current treatment for hypertension or kidney disease, or pregnancy.

Experimental design

Baseline blood pressure was measured on an occasion separate from the time of the screening measures (to avoid regression to the mean during the trial). Randomization occurred after a 1-wk run-in in which a placebo was administered and compliant participants were identified. Compliant participants (those who were given a placebo by the nurse ≥3 of 5 school days) were stratified by sex and age, rank ordered by baseline SBP, and then randomly assigned within pairs formed by the rank ordering to either the calcium or placebo group.

Participants and study personnel were blinded to treatment condition. The calcium and placebo were provided by Marion Laboratories, Kansas City, MO. Supplementation consisted of 1.5 g elemental Ca/d from 3.75 g CaCO3/d administered during lunch on each school day by a school nurse. Glucose placebo tablets were identical in color and shape. Blood pressure was measured at weeks 2, 4, and 8 of the trial. (The planned measurements at 6 wk were interrupted by the Los Angeles riots in the first year of the study and were discontinued.) Follow-up examinations were conducted at the conclusion of each 8-wk supplementation period. Participants were invited to continue in a crossover study after a washout period of 3–12 mo. The 9-wk trial schedule (1 wk run-in, 8 wk supplementation) was fitted into fall and spring semesters during the period from September 1991 to May 1993.

Measurements

At baseline and at the follow-up session at 8 wk, a general questionnaire and a food-frequency questionnaire were completed; blood pressure, radial pulse, height, weight, and physical fitness test (after the blood pressure measurement) were determined; and blood was drawn (on a separate day) for clinical chemistry tests. In addition, blood pressure was measured at the 2- and 4-wk follow-ups. An interview was conducted at 2, 4, and 8 wk to determine side effects. Three-day food records were collected during the intervention from a subsample of subjects to validate the food-frequency questionnaire.

Blood pressure

Blood pressure was measured during the school day by certified observers according to American Heart Association guidelines (34, 35). Seated SBP and diastolic (Karotkoff-5) blood pressures (DBP) were measured on the right arm after the student had been sitting quietly for 5 min. Two auscultatory measures with a standard mercury sphygmomanometer were separated by 2 min. A different observer repeated the procedure after 10 min, yielding a total of 4 measurements. These 4 readings were averaged for purposes of analysis.

Dietary assessment

Semi-quantitative food-frequency questionnaires were completed at the baseline and follow-up examinations. The food-frequency questionnaire was a modification of an instrument developed by Willett and others at the Harvard Public Health Group, versions of which have been used with adults in a variety of studies (36, 37). This “young adult” questionnaire was designed to be self-administered by children and adolescents in the 10–18-y age range from a variety of racial groups (38). The nutrient analysis database is derived from the US Department of Agriculture Handbook no. 8 series augmented with information from current food-composition tables, journals, and manufacturers.

Before use of the food-frequency questionnaire in this study, a pilot test was conducted in 46 African American volunteers (24 females, 22 males). These subjects attended the same high schools in which the trial would be conducted. The goal of the pilot study was to determine whether the 141-item food list included the most commonly eaten foods and to identify those that contributed significantly to the nutrient intake of this adolescent, African American population (39).

As a result of the pilot test, participants in the main study were given additional instructions for completing the food-frequency questionnaire. These instructions focused on how to calculate the average intake for a food over a 1-y time period and how to report composite foods such as hamburgers or casseroles. The questionnaires were reviewed for completeness and obvious errors at the time they were collected.

Midway between administration of the baseline and follow-up food-frequency questionnaires, a subgroup of subjects (n = 84) completed three 24-h diet records (2 weekdays and 1 weekend day). These records were then used to validate the food-frequency questionnaire. Study participants in the validation study were trained in diet record procedures, including determination of weight and volume. The records were reviewed by a dietitian for food type and portion size accuracy as the records were submitted by the participants. Foods were coded by the record collectors and coding was verified by a dietitian supervisor. Analysis of the records was performed by using the Nutrient
Analysis System (40). The database for the Nutrient Analysis System was the National Heart, Lung, and Blood Institute Food Table 10 from the Nutrition Coordinating Center (Minneapolis). The database was updated to include all foods, specific to brand name and portion size, reported to be eaten by study participants.

Data analysis

The first stage of analysis was to estimate carryover effects in the crossover design (41). Baseline blood pressure after crossover was regressed on intervention condition before crossover. No significant carryover effects were detected.

The main and interactive effects of calcium supplementation on seated blood pressure were analyzed with a model that incorporated all data from subjects who completed an 8-wk trial period (42). The primary dependent variable was the change from baseline to the average of the 3 follow-up blood pressure measurements (at 2, 4, and 8 wk). The statistical model can be specified by the following equation:

$$\Delta BP_{ij(t)} = \alpha_{i(j)} + \beta X + \gamma_i Z + \gamma_{ij} XZ + \delta_i + \xi_{ij(t)}$$

where $i$ is 1,...,116 and indicates subject; $j$ is 0, 1, or 2 and indicates the crossover period (where 0 indicates the initial period); and $g$ is 1, 2, or 3 and indicates groups defined by the number of crossover periods completed. Group 1 completed only one 8-wk trial period, group 2 completed 2 trial periods (initial plus 1 crossover), and group 3 completed 3 trial periods (initial plus 2 crossovers). The variable $X$ indicates experimental condition (placebo or calcium). The variable $Z$ is $-1$, 0, or 1 and is a tertile measure of calcium intake from the diet (g/MJ). The product $XZ$ is the interactive term (df = 1) used to determine the significance of the interaction; this specification assumes a linear interaction, so 2 interaction terms (df = 2, allowing for nonlinearity) were used to estimate intervention effects within dietary calcium strata. The residuals were modeled such that they could be partitioned into 2 components: random subject effects, $\delta_i$, and disturbances, $\xi_{ij(t)}$, where these 2 components are not correlated with one another or with the independent variables. The regression coefficients, including the main effect $\beta$ and interactive effect $\gamma_{ij}$, were constrained to be equal across groups and crossover periods. These constraints imply the assumption that crossover observations are missing at random (43). The main effects were estimated without inclusion of the interactive variables in the model.

The constraint that $\beta$ is constant over periods was tested by relaxing this constraint. For the main effect of the intervention on DBP, the goodness-of-fit chi-square test indicated an adequate fit of the model with the data ($\chi^2 = 9.31$, df = 10, $P = 0.50$). Relaxing the constraint on $\beta$ over periods reduced the fit of the statistic slightly ($\chi^2 = 8.38$, df = 8, $P = 0.40$). The difference between the 2 models was not significant ($P = 0.63$), indicating that the assumption of equal effects over periods is consistent with the data.

Secondary analyses included estimates at separate follow-ups and inclusion of covariates (age, sex, and body mass index or baseline blood pressure). Variables were estimated by maximum likelihood assuming multivariate normality (44, 45). Note that this analysis model takes into account any covariance of repeated measurements across periods of the crossover design. A preliminary analysis, which treated the observations as coming from a parallel design, reached conclusions concerning the interaction effects similar to those presented here but had less statistical power (46).

Null hypotheses were tested with two-tailed significance of 5% when there was no a priori directional hypothesis. In the case of main effects and interactions with dietary calcium intake, directional hypotheses were tested with a one-tailed $\alpha$ of 5%.

RESULTS

With multiple counting of crossovers as separate subject observations, a total of 234 trial observations were randomized to experimental conditions. Of these trial observations, 197 (84%) completed the baseline and the 8 wk follow-up measurements. These 197 trial observations were derived from 116 individuals. Of these 116 individuals, 55 completed 1 trial period, 41 completed 2 trial periods, and 20 completed 3 trial periods. Interim blood pressure measurements (after 2 or 4 wk of supplementation) were missing for 4 subjects. Acceptable dietary calcium measures were available for 192 trial observations from 113 individuals (54, 39, and 20 individuals completing 1, 2, and 3 trial periods, respectively).

At baseline, there were no significant differences between the treatment and placebo groups for mean age, height, weight, body mass index, or blood pressure (Table 1). When crossover observations were excluded (analyzing differences between groups at the baseline examination in the first period), there was a significant difference in mean DBP between groups (calcium: 69.1 mm Hg; placebo: 65.7 mm Hg; $P = 0.03$, two-tailed $t$ test). The crossover thus achieved baseline equivalence of groups for DBP.

Attrition of boys was greater in the placebo group than in the calcium group, but the difference was not significant. Boys had higher blood pressure readings (119.7/67.8 mm Hg) than girls (113.8/66.7 mm Hg) at entry into the study. There was regression to the mean from the screening blood pressure measurements to baseline (data not shown), but no significant regression from baseline to follow-up (see change in placebo group in Table 2).

The criterion for good compliance was consumption of ≥75% of the supplements provided by the nurses on school days.

**TABLE 1**

Baseline characteristics of participants by intervention conditions: calcium supplementation or placebo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Calcium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>15.91 ± 1.03 [101]²</td>
<td>15.86 ± 0.98 [96]</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.69 ± 0.09 [101]</td>
<td>1.69 ± 0.10 [96]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.82 ± 14.41 [101]</td>
<td>68.91 ± 14.84 [96]</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.92 ± 4.52 [101]</td>
<td>24.13 ± 4.56 [96]</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)³</td>
<td>67.19 ± 8.41 [101]</td>
<td>65.47 ± 8.93 [96]</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)³</td>
<td>116.36 ± 8.66 [101]</td>
<td>115.89 ± 8.58 [96]</td>
</tr>
<tr>
<td>Dietary calcium intake (g/MJ)</td>
<td>0.086 ± 0.033 [98]</td>
<td>0.084 ± 0.031 [91]</td>
</tr>
<tr>
<td>Dietary potassium intake (g/MJ)</td>
<td>0.28 ± 0.064 [99]</td>
<td>0.28 ± 0.07 [92]</td>
</tr>
<tr>
<td>Sodium intake (g/MJ)</td>
<td>0.25 ± 0.05 [98]</td>
<td>0.24 ± 0.06 [91]</td>
</tr>
<tr>
<td>Total energy intake (MJ/d)</td>
<td>13.7 ± 11.6 [99]</td>
<td>13.0 ± 9.2 [92]</td>
</tr>
<tr>
<td>Percentage female (%)</td>
<td>51 [101]</td>
<td>61 [96]</td>
</tr>
</tbody>
</table>

¹According to two-tailed $t$ tests, there were no significant differences in mean baseline values between the calcium and placebo groups; the $t$ test assumed independent samples, although some measurements were repeated.

²$\bar{x} \pm SD; n$ in brackets: those listed include single or crossover observations of 65 female and 51 male individuals.

³Average of 4 measurements by 2 observers using a standard sphygmomanometer.
Eighty-two percent of subjects met this criterion. Compliance rates at 8 wk were comparable across the calcium and placebo groups (80% and 83%, respectively), and across girls and boys (80% and 84%, respectively). Potential adverse effects of calcium supplementation (diarrhea, upset stomach, or constipation) were reported more frequently in the calcium (31%) than in the placebo (24%) condition. However, this difference was likely to have occurred by chance ($P > 0.2$).

The correlation between estimates of calcium intake from the food-frequency questionnaire and 3-d records was 0.26 ($n = 80$, $P = 0.05$) at baseline and 0.40 ($n = 80$, $P < 0.05$) at the examination at 8 wk. The correlations remained significant after energy intake was adjusted for (baseline: $0.27$, $P < 0.05$; examination at 8 wk = 0.34, $P < 0.05$). These results support the validity of the food-frequency questionnaire for the measurement of calcium intake. Note, however, that total energy intake was inflated in the food-frequency questionnaire relative to the 3-d record. After values were adjusted to the energy intake measured in the records, the average intake of calcium at baseline was estimated at 0.85 g/d. The major food source of calcium was milk (30%), with smaller proportions coming from pizza, other foods containing cheese (eg, nachos, tacos), and other foods containing milk (eg, milkshakes, hot chocolate).

**Calcium supplementation effects**

Changes in blood pressure within the calcium and placebo conditions and net effects across conditions are given in Table 2. DBP averaged over the 3 examinations was significantly reduced in the calcium condition relative to participants receiving placebo. The net effect was largest at 4 wk; however, differences in the calcium condition relative to participants receiving placebo. There was no evidence of an intervention main effect on SBP. Adjustment for covariates and restriction of the analysis to subjects with good compliance (data not shown) did not alter the pattern of findings for SBP or DBP. Inclusion of blood pressure readings taken at the 4 examinations with inadequate measurement of dietary calcium yielded an estimate of the net effect of calcium supplementation on DBP ($−1.9 ± 1.1$ mm Hg; $P = 0.04$, one-tailed $t$ test) similar to that in Table 2.

The interaction between the calcium effect on DBP and tertile of calcium intake from the diet was statistically significant ($P = 0.003$). Net intervention effects were then estimated within tertiles of dietary calcium intake as measured by the average of the intake results from the baseline and follow-up food-frequency questionnaires; if one of these measures was missing, the available measurement was used. Results of these analyses are presented in Table 3 and depicted in Figure 1. Note the monotonic increase in the hypotensive effect of calcium with decreasing calcium intake from food. The covariate-adjusted net effect in the group with the lowest calcium intake ($−5.0 ± 1.6$ mm Hg) was significantly different from zero ($P = 0.002$, one-tailed $t$ test) and significantly different from the net effect in the highest calcium intake tertile ($P = 0.004$, one-tailed $t$ test). Results are comparable with or without covariate adjustment.

In addition to the estimates presented in Tables 2 and 3, effects were estimated by using 2 additional regression models. In the first model, body mass index was replaced with baseline blood pressure as a time-varying covariate (between crossover periods). The resulting estimates of calcium effects on DBP were $−2.5 ± 1.1$ ($P = 0.01$, one-tailed $t$ test), $−1.4 ± 1.1$, and $0.4 ± 1.3$ mm Hg across tertiles of dietary calcium. In the second model, the repeated nature of observations in the crossover design was ignored and data were analyzed as though from a parallel design (46). The resulting estimates of intervention effects on DBP were $−4.8 ± 2.1$ ($P = 0.01$), $1.4 ± 2.2$, and $−1.4 ± 2.1$ mm Hg across the 3 tertiles of dietary calcium. These alternative approaches to

### Table 2

<table>
<thead>
<tr>
<th>Without adjustment</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Average$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium group</td>
<td>$2.54 ± 0.88$</td>
<td>$−1.14 ± 1.04$</td>
<td>$−1.35 ± 0.77$</td>
<td>$−0.01 ± 0.65$</td>
</tr>
<tr>
<td>Placebo group</td>
<td>$1.83 ± 0.59$</td>
<td>$−0.16 ± 0.68$</td>
<td>$−2.09 ± 0.60$</td>
<td>$−0.15 ± 0.48$</td>
</tr>
<tr>
<td>Net effect</td>
<td>$0.71 ± 1.06$</td>
<td>$−0.98 ± 1.24$</td>
<td>$0.74 ± 0.98$</td>
<td>$0.16 ± 0.81$</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium group</td>
<td>$1.03 ± 1.02$</td>
<td>$−2.34 ± 1.01^*$</td>
<td>$−4.25 ± 1.10^*$</td>
<td>$−1.79 ± 0.87^*$</td>
</tr>
<tr>
<td>Placebo group</td>
<td>$1.76 ± 0.82$</td>
<td>$1.42 ± 0.81$</td>
<td>$−5.75 ± 0.72^*$</td>
<td>$0.21 ± 0.63$</td>
</tr>
<tr>
<td>Net effect</td>
<td>$−0.72 ± 1.31$</td>
<td>$−3.76 ± 1.29^*$</td>
<td>$−1.68 ± 1.31$</td>
<td>$−2.00 ± 1.08^*$</td>
</tr>
<tr>
<td>Adjusted for age, sex, and baseline BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium group</td>
<td>$2.64 ± 0.86^*$</td>
<td>$−1.12 ± 1.02$</td>
<td>$−1.34 ± 0.76$</td>
<td>$0.12 ± 0.64$</td>
</tr>
<tr>
<td>Placebo group</td>
<td>$1.84 ± 0.60$</td>
<td>$−0.17 ± 0.69$</td>
<td>$−2.08 ± 0.62^*$</td>
<td>$−0.15 ± 0.49$</td>
</tr>
<tr>
<td>Net effect</td>
<td>$0.80 ± 1.05$</td>
<td>$−0.95 ± 1.23$</td>
<td>$0.74 ± 0.98$</td>
<td>$0.26 ± 0.81$</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium group</td>
<td>$0.92 ± 1.02$</td>
<td>$−2.14 ± 0.99^*$</td>
<td>$−4.19 ± 1.07^*$</td>
<td>$−1.82 ± 0.87$</td>
</tr>
<tr>
<td>Placebo group</td>
<td>$1.77 ± 0.82^*$</td>
<td>$1.42 ± 0.81$</td>
<td>$−2.56 ± 0.73^*$</td>
<td>$0.22 ± 0.64$</td>
</tr>
<tr>
<td>Net effect</td>
<td>$−0.85 ± 1.31$</td>
<td>$−3.57 ± 1.28^*$</td>
<td>$−1.62 ± 1.29$</td>
<td>$−2.04 ± 1.08^*$</td>
</tr>
</tbody>
</table>

$^1$SE. $n = 192$ trial observations from 113 separate individuals.

$^2$Change from baseline for average blood pressure over 3 follow-ups (weeks 2, 4, and 8).

$^*$Significantly different from zero (two-tailed $t$ test); significant net effect (one-tailed $t$ test), $P < 0.05$. 

---

CALCIUM AND BLOOD PRESSURE IN BLACK ADOLESCENTS 651
Net effects of calcium supplementation on blood pressure by tertile of dietary calcium intake

<table>
<thead>
<tr>
<th>Dietary calcium intake (g/MJ)</th>
<th>Without covariate adjustment</th>
<th>Adjusted for age, sex, and baseline BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>Low (0.024–0.067)</td>
<td>−0.42 ± 1.54</td>
<td>−0.59 ± 1.53</td>
</tr>
<tr>
<td>Medium (0.069–0.091)</td>
<td>1.31 ± 1.54</td>
<td>1.22 ± 1.53</td>
</tr>
<tr>
<td>High (0.093–0.217)</td>
<td>1.27 ± 1.65</td>
<td>1.63 ± 1.61</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>−4.56 ± 1.89</td>
<td>−4.72 ± 1.92</td>
</tr>
<tr>
<td>Low (0.024–0.067)</td>
<td>−8.46 ± 1.90</td>
<td>−8.11 ± 1.89</td>
</tr>
<tr>
<td>Medium (0.069–0.091)</td>
<td>−4.28 ± 1.84</td>
<td>−4.16 ± 1.80</td>
</tr>
<tr>
<td>High (0.093–0.217)</td>
<td>2.02 ± 2.05</td>
<td>2.32 ± 2.15</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The current study found that daily supplementation with 1.5 g Ca/d lowered DBP in African American adolescents with a low intake of calcium from the diet (Figure 1). The net mean (±SE) was significant reduction in blood pressure observed in the low dietary calcium group.

There is also evidence of an interaction between the effect of calcium supplementation on SBP and dietary calcium intake. The interaction was significant with or without adjustment for covariates and a nonsignificant blood pressure–lowering effect was observed in the lowest tertile of dietary calcium. However, the net effects within dietary calcium groups are symmetrically distributed about the null, so that the pressure-lowering effect in the low calcium intake group was countered by a comparable pressure increase in the upper dietary calcium group.

Interactions between the calcium effect and dietary intake of sodium and potassium were also assessed. Neither interaction was significant for DBP or SBP. However, as hypothesized, calcium supplementation effects on DBP were larger in the high-sodium and low-potassium intake tertiles. The net effects of calcium were −1.3 ± 1.7 and −5.0 ± 1.7 mm Hg in the upper and middle sodium tertiles and 0.0 ± 2.1 mm Hg in the lower sodium calcium intake tertile. For potassium intake, the net effect of calcium supplementation was 0.4 ± 1.6 mm Hg in the upper tertile of potassium intake and −4.0 ± 1.6 and −3.0 ± 2.0 mm Hg in the lower tertiles. Thus, calcium supplementation tended to show a lowering effect on DBP if the diet was high in sodium or low in potassium, but these differences were not significant.

Serum concentrations of ionized and total calcium were available at baseline and the examination at 8 wk for a subgroup of subjects (n = 112, with multiple counting of crossovers). Baseline means (±SDs) were 2.42 ± 0.12 mmol/L for total and 1.25 ± 0.04 mmol/L for ionized calcium. No significant net effects of the calcium intervention on ionized calcium concentrations were detected for the whole group or within dietary calcium tertiles. However, total serum calcium was significantly greater in the lowest tertile of dietary calcium (net effect = 0.08 ± 0.03 mmol/L; P = 0.01, two-tailed t test), whereas there was little change in the upper 2 tertiles (combined net change of −0.02 ± 0.02 mmol/L).

**FIGURE 1.** Net effect of calcium supplementation (1.5 g/d) on systolic (SBP) and diastolic (DBP) blood pressure over 8 wk of intervention by tertile of dietary calcium intake. Estimates are adjusted for age, sex, and BMI. The net change is the difference between the calcium and placebo groups in blood pressure change from baseline to the follow-up examination. Follow-up blood pressure was the average of measures after 2, 4, and 8 wk of intervention. Dietary calcium was measured with food-frequency questionnaires administered at baseline and at 8 wk. The one-tailed P values are for the interaction of treatment with dietary calcium intake tertile (linear interaction term). Error bars are ±SE. Sample sizes are 64 trial observations per tertile (total of 192 observations from 113 individuals).
duction in DBP with calcium supplementation was 4.9 ± 1.6 mm Hg (5.0 ± 1.6 mm Hg with covariate adjustment) in adolescents in the bottom tertile of calcium intake from diet. Subjects in this bottom tertile also showed an increase in serum total calcium, suggesting that they were the subgroup with greatest physiologic response to the increased intake of calcium.

Calcium supplementation effects on SBP showed an interaction with dietary calcium similar to that observed for DBP (Figure 1). However, in contrast with DBP, the combined effect across dietary calcium concentration was close to null. A small SBP-lowering effect was observed in the low calcium intake group (−1.3 ± 1.2 mm Hg with covariate adjustment), but the net effect in the high calcium intake group was of comparable magnitude in the hypertensive direction (1.9 ± 1.3 mm Hg).

These findings are partially consistent with 2 related trials in younger subjects. A trial in Holland in young adults aged 16-29 y found a net reduction of 3.1 ± 1.7 and 2.4 ± 1.9 mm Hg in DBP after 6 and 12 wk of supplementation with 1.0 g Ca/d as calcium citrate (47). As in the current study, subjects had been screened for moderately elevated blood pressure; however, dietary intake was not measured. Similar to the current findings, no evidence of an effect on SBP was found in the Dutch study.

A recently reported pilot study in children (61% were black) aged 9-13 y in Boston investigated the effect of 0.6 g Ca/d as calcium citrate malate (48). Although no significant main effects of the intervention were found, there was a monotonically larger effect on SBP as dietary intake of calcium decreased (net effect of −3.5 ± 2.5 mm Hg in the lowest quartile). However, this trend was not observed for DBP. Thus, our findings and those of Grobbee and Hofman (47) are corroborative concerning calcium effects on DBP in adolescents and young adults. The findings of Gillman et al (48) support the interaction with dietary intake, but not for DBP. This latter inconsistency may have been the result of the use of an automated blood pressure device in Gillman et al’s study (49).

Recent meta-analyses of calcium supplementation trials in adults indicate that effects on blood pressure are varied. Bucher et al (19) found that net reductions in blood pressure averaged 5.4 ± 1.2 mm Hg for SBP and 3.4 ± 0.9 mm Hg for DBP in pregnant women. Substantial preventive effects on the incidence of new hypertension were also found, and the magnitude of this effect interacted with age. Relative to placebo, calcium supplementation reduced the risk of hypertension by 36% (95% CI: 5%, 57%) in trials with subjects on average ≥20 y of age and by 79% (95% CI: 62%, 89%) in trials in younger women. However, a recent large trial in pregnant women found only a small reduction in the incidence of hypertension and no significant reduction in blood pressure (20). A similar meta-analysis of trials in groups other than pregnant women found smaller aggregate effects of calcium supplementation on blood pressure: −1.3 ± 0.5 mm Hg for SBP and −0.2 ± 0.3 for DBP (25). Heterogeneity of the supplementation effect by age of subjects was not reported in this meta-analysis.

The effects observed in the current study on DBP in African American adolescents with low intakes of calcium from the diet may be specific to the increased requirements for calcium resulting from rapid growth or hormonal processes associated with adolescence. The major limitation on interpretation of the results from the current study is the failure to detect a blood pressure-lowering effect of calcium supplementation on SBP in persons with low intake of calcium from the diet. The meta-analyses cited above indicate that effects of calcium supplementation in pregnant and nonpregnant groups should be larger on SBP than on DBP (19, 25). Furthermore, the effects on blood pressure of a high-calcium diet (rather than supplementation) in the Dietary Approaches to Stop Hypertension (DASH) trial (50) were also greater on SBP than on DBP. The net effect of calcium on SBP in the current study was −1.3 ± 1.2 mm Hg in the lowest tertile of calcium intake. The size of this effect is similar to −1.3 ± 0.5 mm Hg, which was observed in nonpregnant populations (25).

Several mechanisms have been proposed to explain a hypotensive effect of calcium supplements in hypertensive rats and humans. The hypothesized effects of calcium supplementation include lowered parathyroid hormone and serum dihydroxycholecalciferol, enhanced urinary excretion of calcium and phosphate, enhanced excretion of sodium, dampened membrane permeability, and increased intracellular cell membrane calcium-binding capacity (51). The current finding of a hypotensive effect of calcium supplementation on DBP only among subjects with a high intake of sodium offered some indirect support for the enhanced sodium excretion hypothesis.

The finding of a blood pressure-lowering effect only in adolescents with a low intake of dietary calcium may be explained by recent evidence concerning a polymorphism (b and B) of the vitamin D receptor gene. Dawson-Hughes et al (27) reported that calcium supplementation compensated for reduced calcium absorption efficiency associated with the bb allelic variant of this gene. Differences between the bb and BB allelic groups in calcium absorption efficiency and plasma dihydroxycholecalciferol concentrations were found at low calcium intakes (300 mg/d) but not at higher intakes (1500 mg/d). Low calcium intake was associated with a larger increase in plasma dihydroxycholecalciferol concentrations in the bb than in the BB allelic group. Calcium supplementation may thus affect calcium absorption efficiency and circulating concentrations of dihydroxycholecalciferol in genetic subgroups of the population when dietary calcium intake is low. Such a model would imply small and inconsistent effects on blood pressure in calcium supplementation trials.

Another explanation from the small and inconsistent effects on blood pressure in calcium supplementation trials was suggested by the results of the DASH trial (50). Among moderately hypertensive subjects, highly significant net effects of −11.4 and −5.5 mm Hg on SBP and DBP, respectively, were achieved over 8 wk with a “combination” diet high in calcium (from low-fat dairy products), fruit, and vegetables and low in fat and saturated fat (compared with a typical American control diet). A plausible explanation of these strong findings is that blood pressure-lowering effects of calcium and other nutrients combined additively or synergistically. Calcium supplementation alone, then, may achieve only a small portion of the antihypertensive effect of increased consumption of foods rich in calcium.

Results of the DASH trial were also reported separately for minority (primarily black) and nonminority participants with hypertensive and nonhypertensive groups combined, and there was a nonsignificant trend toward stronger effects in the minority group. Net effects on SBP were −6.8 and −3.0 mm Hg and on DBP were −3.5 and −2.0 mm Hg in the minority and nonminority groups, respectively. These findings suggest that the blood pressure response to increased intake of dairy products may be greater in African Americans. Finally, the blood pressure-lowering effects in DASH were achieved after 2 wk of the combination diet and then maintained throughout the trial.
Our findings provide limited support for the hypothesis of a preventive benefit of calcium supplementation in persons with low calcium intake from the diet. Although available data are not compelling concerning long-term benefit, the low cost and safety of calcium supplementation, together with potential benefits from prevention of other health problems (52–54), warrant further research on the potential of calcium supplements as a hypertension prevention strategy. In addition, the results from the particular population studied in this trial suggest that this strategy may be effective in African Americans, a group with dramatically increased risk of hypertension (28–31) and its sequelae (55, 56).

We acknowledge the contributions of the following to this project: Dora Frazier; Margaret Pierre; Patricia Irvine; Pat Lachelt; Vera Vignes, Superintendent of the Pasadena City Schools; the Pasadena Prevention Project Community Advisory Board; and especially the students and staff of the participating schools.

REFERENCES