Blood pressure and calcium intake are related to bone density in adult males

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Based on the premise that elevated blood pressure and low bone mass have both been associated with poor Ca nutriture and disturbances in Ca metabolism, a cross-sectional study was employed to determine if blood pressure and dietary Ca intake were significantly related to bone mass. Forty-seven men between 24–77 years of age with blood pressure values ranging from normal to mildly elevated comprised the study group. Blood pressure was measured with a random-zero sphygmomanometer. Bone mineral content (BMC) and density (BMD) of the hip, spine and total body were measured with dual-photon absorptiometry. Dietary intake and physical activity were also assessed. Multiple linear regression analysis was used for statistical analysis. After adjusting for known confounding variables (age, BMI, Ca intake, and others) diastolic blood pressure was negatively related to BMC ($P \leq 0.05$) and BMD ($P \leq 0.01$) of the total body, trochanteric region ($P < 0.01$) and Ward's triangle ($P < 0.05$), and to BMC of the femoral neck ($P < 0.05$) and lumbar spine, although the latter was just shy of statistical significance ($P = 0.058$). Systolic blood pressure was negatively related to trochanteric BMD ($P = 0.04$) and BMC ($P = 0.06$). Ca intake was positively related to total body BMD ($P = 0.005$), and BMC of the lumbar spine ($P = 0.05$). In this population of men, Ca intake was a positive predictor, and blood pressure was a negative predictor of regional measures of bone mass. These findings support the concept that independent of age, BMI and Ca intake, elevated blood pressure varies indirectly with bone mass and density, known predictors of osteoporotic fractures. Future studies are needed to determine whether elevated blood pressure is causally related to the development of low bone mass, and what role dietary Ca plays in that pathway.

Blood pressure: Calcium intake: Bone mass

Hypertension and osteoporosis are both chronic conditions that are associated with poor Ca nutrition (National Institutes of Health, 1994; Bucher *et al.* 1996). Hypertensive individuals manifest a number of disturbances in Ca metabolism that are also consistent with a metabolic profile leading to enhanced bone resorption and subsequent bone loss. These disturbances include elevated parathyroid hormone levels, increased urinary Ca excretion, abnormal gut absorption of Ca, and deficient dietary Ca intake (McCarron, 1989; Hamet, 1995). While rat models of hypertension exhibit excessive bone loss, abnormal bone architecture and reduced levels of bone mineral mass compared with normotensive controls (Izawa *et al.* 1985; Lucas *et al.* 1986; Metz *et al.* 1988, 1990; Yamori *et al.* 1991; Wang *et al.* 1993), the relationship between blood pressure and bone mineral density (BMD) in a human population has not been previously explored. The objective of the present study was to examine the relationship between blood pressure and regional measures of bone mass in a population with blood pressures ranging from normal to mildly elevated.

Subjects and methods

Subjects

The subjects for this study were participants in a clinical trial that was specifically recruiting individuals with both normal and mildly elevated blood pressure values. Informed consent was obtained from each subject, and all procedures were approved by the Institutional Review Board of the Oregon Health Sciences University. The procedures followed were in accord with the ethical standards of the responsible committee on human experimentation.

Forty-seven men, aged 24–77 years, with blood pressures ranging from normal to mildly elevated, participated in the study. Elevated blood pressure was defined as mean arterial pressure greater than or equal to 105 mmHg. During the run-in period blood pressure medication was withheld for a minimum of 4 weeks before randomization to treatment limbs, either active agent or placebo. Participants who had previously taken thiazide diuretics or oral or topical steroids were excluded from the study. Additional exclusion criteria included secondary hypertension of any aetiology, weight >150 % of ideal body weight according to the Metropolitan Life height and weight tables, chronic alcoholism or drug addiction, congestive heart failure, emphysema, myocardial infarction within the last year, renal disease, history of gastrectomy, hypogonadism, and any disease or concurrent medication use known to affect Ca balance.

Procedures

Blood pressure in the sitting position was measured with a random-zero sphygmomanometer. Blood pressure was measured after 5 min rest and recorded at 1 min intervals for 4 min with the arm at cardiac level. The average of four readings was used. BMD was measured once at the lumbar spine and proximal femur, and in the total body, with dual-photon absorptiometry using a Lunar DP4 dichromatic bone densitometer (Lunar Corporation, Madison, WI, USA) with a ^{153}Gd source. Six 24 h recalls were solicited over the study period. Dietary information was collected by a registered dietitian who asked participants to recall in detail their dietary intake over the previous 24 h period. Food models were used as prompts. Participants were not told in advance that dietary information would be solicited on specific visits. Dietary data were analysed using a licensed copy of the University of Minnesota Nutrition Coordinating Center Nutrition Data System. Current leisure-time physical activity (h/week) was estimated from questionnaire responses.

Statistical analysis and model selection

SAS$^{©}$ for personal computers (1987; Statistical Analysis Systems Inc., Cary, NC, USA) was used for all statistical procedures. Descriptive statistics (means, SD and ranges) were determined for all variables. Verification of normally distributed data was confirmed during the exploratory data analysis phase. Multiple linear regression analysis was used to determine if blood pressure and dietary Ca were significantly ($P < 0.05$) associated with regional bone mineral content (BMC) or BMD variables while adjusting for confounding variables. Each bone variable was treated as a dependent variable and all potential predictors and covariates were treated as independent variables, and were regressed *v.* the dependent variables. Independent variables selected for inclusion in the models were determined both by theoretical associations to bone mass and through strong relationships observed during exploratory data analysis. Because of the small sample size for the number of individuals with complete data (n 47), the number of variables included in each model was limited to a maximum of five. Age and BMI were used in all models because of their well-known associations with bone mass; systolic

blood pressure (SBP) and diastolic blood pressure (DBP) were used separately in otherwise similar models. Ca, Ca^2, alcohol, and physical activity were retained in models if they contributed a reasonable level of explanatory power ($P \leq 0.30$). The same models were used for each regional bone site. No two independent variables were correlated above 0.29, with the exception of Ca and Ca^2, which were expected to be highly correlated. A quadratic term for Ca intake (Ca^2) was included in model selection because of its known association with BMD as a 'threshold nutrient', i.e., the association is non-linear (Matkovic & Heaney, 1992). Squared semi-partial (type II) correlation coefficients were determined for each independent variable in order to evaluate the relative proportion of variance that could be explained by each variable per model, while simultaneously controlling for the other independent variables in the model. The following models were used:

$$\text{total body BMD or BMC} = \text{intercept} + \beta_1.\text{age} + \beta_2.\text{BMI}$$
$$+ \beta_3.\text{ca} + \beta_4.\text{ca}^2 + \beta_5.\text{DBP or } \beta_5.\text{SBP} + e,$$
$$\text{trochanteric BMD or BMC} = \text{intercept} + \beta_1.\text{age} + \beta_2.\text{BMI}$$
$$+ \beta_3.\text{physical activity} + \beta_4.\text{DBP or } \beta_4.\text{SBP} + e,$$
$$\text{femoral neck BMD or BMC} = \text{intercept} + \beta_1.\text{age}$$
$$+ \beta_2.\text{BMI} + \beta_3.\text{alcohol} + \beta_4.\text{DBP or } \beta_4.\text{SBP} + e,$$
$$\text{Ward's triangle BMC or BMD} = \text{intercept} + \beta_1.\text{age}$$
$$+ \beta_2.\text{BMI} + \beta_3.\text{alcohol} + \beta_4.\text{DBP or } \beta_4.\text{SBP} + e,$$
$$\text{lumbar spine (L2–4) BMC or BMD} = \text{intercept} + \beta_1.\text{age}$$
$$+ \beta_2.\text{BMI} + \beta_3.\text{ca} + \beta_4.\text{ca}^2 \text{ DBP or } \beta_4.\text{SBP} + e,$$

where ca is Ca intake and e is random error.

Results

Descriptive statistics for the study population are shown in Table 1.

Multivariate statistics for the association between DBP, dietary Ca, and regional BMD and BMC are shown in Table 2. DBP was negatively ($P \leq 0.05$) related to BMD and BMC of the total body, trochanteric region, and Ward's triangle, and to BMC of the femoral neck. SBP was negatively related to BMD ($P = 0.0430$) and just shy of statistical significance for BMC ($P = 0.0578$) of the trochanteric region in comparable models, but not to the remaining bone measurements. Dietary Ca intake was positively ($P = 0.046$) associated and Ca^2 was negatively associated ($P < 0.04$) with total body BMD and with BMC of the lumbar spine ($P < 0.05$).

Covariates significantly ($P < 0.05$) associated with regional bone measurements in models with DBP included age, BMI, and physical activity level. Age was negatively related to BMD of the Ward's triangle ($P = 0.0034$) and femoral neck ($P = 0.0478$). BMI was positively related to BMC and BMD of the total body, Ward's triangle ($P = 0.058$) and lumbar spine, and to trochanteric BMC ($P < 0.0485$). Activity level was negatively associated with BMD ($P = 0.0297$) and BMC ($P = 0.0475$) of the trochanteric region.

Table 1. Characteristics of the forty-seven subjects in the present study
(Mean values, standard deviations and ranges)

Variable	Mean	SD	Range
Age (years)	50·4	12·8	24–77
BMI (kg/m^2)	27·4	3·7	22·1–35·0
Systolic blood pressure (mmHg)	131·8	13·8	105·5–164·5
Diastolic blood pressure (mmHg)	82·7	9·3	60·0–100·0
Femoral neck BMD (g/cm^2)	1·020	0·167	0·700–1·570
Femoral neck BMC (g)	5·715	1·176	3·200–10·700
Lumbar spine (L2–4) BMD (g/cm^2)	1·343	0·173	1·071–1·862
Lumbar spine BMC (g)	69·59	11·23	51·64–96·64
Total body BMD (g/cm^2)	1·261	0·097	0·949–1·445
Total body BMC (g)	3473·96	456·89	2682·00–4732·00
Trochanteric BMD (g/cm^2)	0·880	0·113	0·650–1·160
Trochanteric BMC (g)	14·107	2·596	8·220–20·870
Ward's triangle BMD (g/cm^2)	0·840	0·197	0·460–1·570
Ward's triangle BMC (g)	2·748	0·953	1·260–7·640
Leisure-time activity (h/week)	11·8	9·5	0·0–40·0
Alcohol intake (g/d)	14·6	23·5	0·0–91·3
Energy intake (kcal/d)	2208·8	508·5	1212·3–3455·8
(kJ/d)	9277·0	2135·7	5091·7–14 514·4
Protein intake (g/d)	88·9	24·5	38·8–155·2
Calcium intake (mg/d)	865·5	323·7	317·8–1610·6
Sodium intake (mg/d)	2790·7	751·1	1313·4–4930·7
Potassium intake (mg/d)	3282·0	826·3	1564·0–5223·3
Magnesium intake (mg/d)	356·8	123·5	163·4–713·0

BMC, bone mineral content; BMD, bone mineral density.

Table 2. Squared semi-partial correlation coefficients (S-PR^2), multiple regression coefficients (β) and standard errors for the association between blood pressure and regional measures of bone mineral density (BMD) and bone mineral content (BMC) in men

(S-PR^2 describes the amount of variation explained in the dependent variable by the predictor variable, whereas β describes the magnitude and the direction of the association between the predictor and dependent variables)

	BMD			BMC		
	S-PR^2	β	SE	S-PR^2	β	SE
Total body						
age	0·030	−0·0015	0·0009	0·002	−1·83	5·23
BMI	0·320	0·0162**	0·0031	0·223	63·65**	17·37
Ca	0·100	0·0005**	0·0002	0·049	1·71†	0·995
Ca^2	0·110	−0·0000**	−0·000001	0·054	−0·0009†	0·0005
DBP	0·090	−0·0035**	0·0013	0·087	−16·06*	7·03
Trochanteric						
age	0·003	−0·0005	0·0013	0·066	0·0561†	0·0297
BMI	0·038	0·0065	0·0046	0·090	0·2303*	0·1049
physical activity	0·097	−0·004*	0·0018	0·078	−0·0816*	0·0399
DBP	0·135	−0·0051**	0·0019	0·181	−0·1374**	0·0441
Femoral neck						
age	0·081	−0·0039*	0·0019	0·011	−0·0103	0·0142
BMI	0·055	0·0114†	0·0068	0·040	0·0694	0·0500
alcohol	0·011	0·0008	0·0010	0·034	0·0097	0·0076
DBP	0·044	−0·0042	0·0028	0·092	−0·0433*	0·0206
Lumbar spine						
age	0·033	0·0016	0·0021	0·019	0·1370	0·1368
BMI	0·153	0·0190*	0·0071	0·073	0·8926*	0·4541
Ca	0·052	0·0007†	0·0004	0·077	0·0525*	0·0260
Ca^2	0·061	−0·000004†	0·000002	0·091	0·00003*	0·0001
DBP	0·037	−0·0036	0·0029	0·070	−0·3526†	0·1838
Ward's triangle						
age	0·158	−0·0065**	0·002	0·018	−0·0107	0·0113
BMI	0·052	0·0130†	0·0072	0·076	0·0771*	0·0395
alcohol	0·019	0·0012	0·0011	0·035	0·0080	0·0060
DBP	0·069	−0·0062*	0·0030	0·090	− 0·0346*	0·0162

DBP, diastolic blood pressure.
* $P < 0.05$, ** $P < 0.005$, † $P \leq 0.10$.

Covariates significantly associated with regional bone measurements in models with SBP included age, BMI, and Ca intake. Consistent with models that included DBP, age was negatively related to BMD of the Ward's triangle ($P=0.0044$) and femoral neck ($P=0.0546$). BMI was positively related to BMC and BMD of the total body ($P \leq 0.004$) and to BMD of the lumbar spine ($P=0.02$). Ca intake was positively associated ($P=0.0058$) and Ca^2 was negatively associated ($P=0.0074$) with total body BMD.

Squared semi-partial correlations are also shown in Table 2. These correlation coefficients provide information on the proportion of variance each predictor variable is able to explain in each of the bone mass variables. Depending on the model, DBP explained between 4 and 18 % of the variation in bone mass measurements. While not appropriate to compare these coefficients across different models, the data do suggest that within models, DBP explains as much of the variance in bone mass as do many of the other variables having a known and significant association with bone mass.

Discussion

The purpose of the present study was to determine the nature of the relationship between blood pressure, dietary Ca and total body and regional measures of bone mass in a male population with normal to mildly elevated blood pressures. The rationale was based on the premise that a subset of individuals with hypertension manifest a disturbed Ca-metabolic profile compatible with consequent loss of bone tissue, a postulate supported by the consistent observation of low BMD or BMC in a number of experimental models of hypertension (Izawa *et al.* 1985; Lucas *et al.* 1986; Metz *et al.* 1988, 1990; Yamori *et al.* 1991; Wang *et al.* 1993). Our findings show that DBP was independently and negatively related to BMD and BMC of the total body and to regional measures of BMD and BMC. SBP was found to be significantly and negatively related to trochanteric BMD, and the association was just shy of statistical significance for BMC.

The observational nature of this study precludes identifying any causal associations between blood pressure and bone mass measurements, i.e. that high blood pressure contributes to bone loss. However, these preliminary findings are indirectly supported by experimental data demonstrating that indices of bone mineral metabolism associated with the metabolic sequelae related to bone loss are also manifest in some individuals with hypertension (Resnick *et al.* 1983; Strazzulo *et al.* 1983; Grobbee *et al.* 1986; McCarron, 1989; Papagalanis *et al.* 1991; Young *et al.* 1992; Hamet, 1995). The most relevant of these disturbances include lower dietary Ca intake, inappropriately lower intestinal absorption of Ca, and increased urinary Ca excretion in the setting of higher circulating parathyroid hormone levels, lower vitamin D_3 concentrations, and reductions in plasma ionized Ca. When dietary Ca intake is sufficient, it may act to lower blood pressure by a direct effect on vascular smooth muscle cells such that the cell's ability to extrude Ca is improved. Similarly, the Ca-regulating hormones have vasoactive properties that

could have an indirect impact on the same cellular functions. Dietary Ca may also affect blood pressure by altering sympathetic nervous system activity, by modifying the metabolism of other electrolytes such as Na or K, or by affecting the central nervous system (Hatton & McCarron, 1994). Although these endpoints were not measured in the present study, the consistency of these metabolic defects observed in previous studies of human essential hypertension is remarkable (Resnick *et al.* 1983; Strazzulo *et al.* 1983; Grobbee *et al.* 1986; McCarron, 1989; Papagalanis *et al.* 1991; Young *et al.* 1992; Hamet, 1995).

An additional line of evidence in support of the present findings comes from rat models of hypertension in which bone mass has been shown to be reduced or metabolically altered compared with normotensive controls (Izawa *et al.* 1985; Lucas *et al.* 1986; Metz *et al.* 1988, 1990; Yamori *et al.* 1991; Wang *et al.* 1993). In addition, human renal stone disease is associated with increased Ca excretion, hypertension, reduced dietary Ca intake and reduced levels of bone mass (Tibblin, 1967; Cirillo & Laurenzi, 1988; Cappuccio *et al.* 1990; Bataille *et al.* 1991; Curhan *et al.* 1993; Jaeger *et al.* 1994). MacGregor & Cappuccio (1993) have also hypothesized that these abnormalities in Ca metabolism in patients with hypertension may contribute to long-term bone demineralization.

Why DBP was a better predictor of bone mass than SBP is uncertain. This finding may reflect the fact that DBP is more dependent on volume status than SBP. Volume-dependent variations, i.e. salt sensitivity, in blood pressure have been shown to be more sensitive to modifications in dietary Ca intake and/or markers of perturbed Ca metabolism compared with volume-resistant blood pressure variations (Yamakawa *et al.* 1992; Weinberger *et al.* 1993). Thus, it follows that total body and regional BMD, an overall marker of Ca status, would be more closely related to DBP than SBP. However, volume-dependent variations in blood pressure regulation were not assessed in the present study.

Covariates significantly related to bone measurements included Ca, Ca^2, BMI, age, and activity level. Of these, variables negatively related to bone measurements included age, Ca^2 and activity level. Results for the negative association between age and bone measurements are consistent with the literature indicating that BMD in general declines with age (Garn *et al.* 1967; Hernandez-Avila *et al.* 1991). Additionally, the negative quadratic term for Ca (Ca^2) indicates that overall, the positive association observed between Ca and total body BMD in this model is non-linear, and that Ca consumption beyond a defined level may offer no additional benefit to BMD. This is consistent with a 'threshold effect' of Ca on BMD which has been previously demonstrated (Heaney, 1992; Matkovic & Heaney, 1992). The negative relationship observed between activity level and trochanteric BMD and BMC seems counterintuitive, but may be a result of life-long exposure of an excessive weight-bearing load received directly to the trochanter.

The positive association between BMI and selected bone measurements is consistent with the well-established notion that BMI is a positive determinant of BMD (Felson *et al.* 1993). While the positive relationship observed in the present study between Ca intake and total body BMD is

consistent with other studies in women and children (Dawson-Hughes *et al.* 1990; Chapuy *et al.* 1992; Johnston *et al.* 1992; Recker *et al.* 1992; Lloyd *et al.* 1993; Reid *et al.* 1993), the relationship between Ca intake and BMD in men is relatively unexplored and these findings are supportive of the limited literature available on Ca and bone health in men (Cooper *et al.* 1988; Holbrook *et al.* 1988; Kelly *et al.* 1990; Orwoll *et al.* 1990).

The present study has several limitations. The study design prevents making causal inferences, and the results cannot be generalized to other populations. In addition, the sample size was small, and some of the control variables were assessed by recall (diet, physical activity), and may lack a high degree of precision as a result. In addition, the method used to measure bone mass, dual-photon absorptiometry, offers less precision than its more contemporary counterpart, dual-energy X-ray absorptiometry (Lees & Stevenson, 1992), particularly in patients with increasing body mass (Martin *et al.* 1993), however, this method still offers high accuracy and adequate clinical precision (Mazess & Barden, 1988). Because these biases would serve to increase variability and misclassification bias, the effect would be a dilutional one; to bias the results in the direction of the null hypothesis. As a consequence, it is possible that the results found in this study are conservative estimates of the strength of the relationships observed. Considering these limitations, and that the hypotheses tested were biologically plausible, the fact that significant results were found suggests the possibility that the relationship between higher blood pressure and reduced bone mass may not be entirely accounted for by other known risk factors. However, a larger sample size in addition to the measurement of biochemical indices of bone mineral metabolism would need to be employed to assess more carefully the relationship between increased arterial pressure and BMD. In fact, it is possible that increases in blood pressure and reductions in BMD are independent pathophysiological expressions of reduced Ca intake, and/or one or more abnormalities of Ca metabolism. Thus, to the authors' knowledge, these data provide the first observation in human subjects, that blood pressure and bone mass are inversely related; further work is needed to confirm these findings, and to explore the nature of this relationship.

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