

High blood pressure and bone-mineral loss in elderly white women: a prospective study

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Summary

Background High blood pressure is associated with abnormalities in calcium metabolism. Sustained calcium loss may lead to increased bone-mineral loss in people with high blood pressure. We investigated the prospective association between blood pressure and bone-mineral loss over time in elderly white women.

Methods We studied 3676 women who were initially assessed in 1988–90 (mean age 73 years [SD 4, range 66–91 years]; mean bodyweight 65.3 kg [11.5]; blood pressure 137/75 mm Hg [17/9]) who were not on thiazide diuretics. Mean follow-up was 3.5 years. Anthropometry, blood pressure, and bone-mineral density at the femoral neck were measured at baseline and bone densitometry was repeated after 3.5 years by dual-energy X-ray absorptiometry.

Findings After adjustment for age, initial bone-mineral density, weight and weight change, smoking, and regular use of hormone-replacement therapy, the rate of bone loss at the femoral neck increased with blood pressure at baseline. In the quartiles of systolic blood pressure, yearly bone losses increased from 2.26 mg/cm² (95% CI 1.48–3.04) in the first quartile to 3.79 mg/cm² in the fourth quartile (3.13–4.45; test for heterogeneity, $p=0.03$; test for linear trend, $p=0.01$), equivalent to yearly changes of 0.34% (0.20–0.46) and 0.59% (0.49–0.69; test for heterogeneity, $p=0.02$; test for linear trend, $p=0.005$). There was no significant interaction with age. The exclusion of women on antihypertensive drugs did not alter the results. For diastolic blood pressure, there was an association with bone loss in women younger than 75 years.

Interpretation Higher blood pressure in elderly white women is associated with increased bone loss at the femoral neck. This association may reflect greater calcium losses associated with high blood pressure, which may contribute to the risk of hip fractures.

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Introduction

Animal, clinical, and some epidemiological evidence suggests that high blood pressure is associated with abnormalities of calcium metabolism, leading to increased calcium losses, secondary activation of the parathyroid gland, and increased movement of calcium from bone.^{1–7} Some of these abnormalities are seen in children and young people^{5,8} and are detected throughout adult life.^{1–4,6,7} If substantial calcium loss related to high blood pressure, which may be due to a defect in the kidney's ability to handle calcium,^{9,10} is sustained over many decades, increased movement of calcium from bone may result in higher rates of mineral loss, thereby increasing the risk of osteoporosis. Metabolic studies in hypertensive rats show that hypercalciuria and ensuing hyperparathyroidism lead to reduced growth and detectable decrease in total bone-mineral content later in life.^{11,12} However, no direct evidence is available in human beings.

We investigated prospectively the relation between blood pressure and bone-mineral loss in elderly white women.

Patients and methods

Study population

Full details of the prospective Study of Osteoporotic Fractures have been published elsewhere.^{13–19} From September, 1986, to October, 1988 (visit 1), 9704 white women aged at least 65 years were recruited for baseline assessment from population-based listings (such as voter's registration lists) in four areas of the USA: Baltimore County, MD; Minneapolis, MN; Portland, OR; and Monongahela Valley (near Pittsburgh), PA. African-American women, women who were unable to walk without the assistance of another person, and women who had bilateral hip replacements were excluded.

During a second assessment (visit 2), between January, 1989, and January, 1991, bone density of the proximal femur was measured with dual-energy X-ray absorptiometry (QDR 1000, Hologic, Waltham, MA, USA) in 8116 women (87% of those alive at that time).¹⁷ In August, 1992, all women were invited to participate in a new assessment that was completed in July, 1994 (visit 4; no bone densitometry measurements were taken at visit 3). 6796 women (77% of those still alive) completed the follow-up assessment. Of these women, 5767 had hip-bone-mineral density measurements at visit 2 and visit 4; 2091 women who reported current or past use of thiazide diuretics at visit 1 or visit 2 were excluded because of primary indication of hypertension by these drugs and their effect on bone density and hip fractures.¹⁵ We report on 3676 white women who had bone densitometry at the proximal femur measured with dual-energy X-ray absorptiometry at baseline (visit 2) and 3.5 years later, and who had not been on thiazide diuretics at the time of the assessment.

Study design

We ascertained several baseline characteristics,^{13–19} including smoking habits, current use of hormone-replacement therapy, and use of antihypertensive medication. We asked women whether they had ever taken diuretics, and requested that they bring all

current medications to the clinic for verification, including diuretics. In addition, pictures of tablets were presented to participants to assist them in recollection of previously prescribed diuretics. Diuretics, including combination drugs, were classified as thiazide diuretics according to American Medical Association guidelines.²⁰ Separate histories were obtained from participants for use of thiazide and non-thiazide diuretics. Chlorthalidone was classified as a thiazide diuretic because its effects on calcium excretion are similar to those of thiazide diuretics. Information on other antihypertensive medications was obtained during follow-up.

During each assessment, bodyweight (after removal of shoes and heavy outer clothing) was measured with a balance-beam scale, and height (after removal of shoes) with a Harpenden stadiometer (Holtain Ltd, Crosswell, Crymych, Dyfed, UK). Height and weight were used to calculate body-mass index. Blood pressure and pulse rate were measured after at least 5 min supine rest in a quiet room by sphygmomanometer with appropriate cuff. Systolic and diastolic blood pressures were taken at Korotkov sounds I and V.

We measured the bone density of the proximal femur by dual-energy X-ray absorptiometry. Methods of bone-mass measurements, densitometry quality-control procedures, and precision of the measurements have been published elsewhere.^{14,17} The yearly rate of change in bone-mineral density was calculated as the difference between baseline and follow-up bone-mineral density divided by the duration of follow-up (in years). The rate of change in proximal femur bone mass is expressed as absolute change in bone mass (mg/cm²) per year and as relative change in bone mass (%) per year.

Statistical analysis

We used correlation analysis (*r* coefficient) to assess the associations between bone-mineral loss and different continuous variables, and ANOVA and ANCOVA for the association between blood pressure (stratified by quartiles of systolic and diastolic blood pressure to generate equal numbers of women in each category) and rate of change in bone-mineral density during follow-up. Differences across blood-pressure strata were tested for heterogeneity and the presence of linear trends. Adjustment was made for age, initial bone-mineral density, baseline weight, weight change, current smoking, and use of hormone-replacement therapy. Interactions with age were also tested in the categories younger than 75 and 75 years or older. Two-sided *p* values are reported.

Results

Participants were generally healthy women (table 1). Few women were smokers and more than 15% were on hormone-replacement therapy. After 3.5 years of follow-up, 16.9% of women were on regular antihypertensive therapy and had a small decline in bodyweight. Mean yearly loss of femoral-neck bone mineral was just over 3 mg/cm², equivalent to a yearly loss of 0.5%.

Absolute and relative femoral-neck bone losses were significantly associated with age (*r*=-0.05, *p*<0.01; *r*=-0.07, *p*<0.001) and baseline systolic blood pressure

Characteristics	
Baseline (visit 1 or 2)	
Age (years)	73 (4)
Weight (kg)	65.3 (11.5)
Height (cm)	159.5 (5.9)
Body-mass index (kg/m ²)	25.6 (4.2)
Systolic blood pressure (mm Hg)	137 (17)
Diastolic blood pressure (mm Hg)	75 (9)
Pulse rate (beats/min)	68 (9)
Femoral-neck bone-mineral density (g/cm ²)	0.636 (0.109)
Current smoker	291 (7.9%)
Hormone-replacement therapy (at visit 2)	571 (15.5%)
Follow-up (visit 4)	
Weight change (kg/year)	-0.04 (1.17)
Yearly femoral-neck bone-mineral density change	
Absolute (mg/cm ²)	-3.2 (11.0)
Percentage (%)	-0.50 (1.72)
Antihypertensive treatment (at visit 4)	623 (16.9%)

Data are means (SD) or numbers (%).

Table 1: Characteristics of women at baseline and follow-up

(*r*=-0.05, *p*<0.01; *r*=-0.05, *p*<0.01). Moreover, current smokers had more bone loss than non-smokers (-0.85% [95% CI -1.04 to -0.65] vs -0.47% per year [-0.53 to -0.41], difference 0.37% [0.17-0.58]), and women on hormone-replacement therapy showed a slower rate of loss (-0.28% [-0.42 to -0.14] vs -0.54% [-0.60 to -0.48] per year, difference 0.26% [0.11-0.41]).

Absolute and the relative yearly rates of change of femoral-neck bone-mineral density increased with baseline systolic and diastolic blood pressure (table 2). Differences in systolic blood pressure were significant. This association was not affected when women on antihypertensive medication (*n*=623) were excluded from the analysis (relative changes by quartiles of systolic blood pressure: first quartile -0.35% per year [-0.47 to -0.23]; second quartile -0.53% per year [-0.63 to -0.43]; third quartile -0.49% per year [-0.61 to -0.37]; fourth quartile -0.64% per year [-0.76 to -0.52]; heterogeneity *p*=0.014, linear trend *p*=0.004).

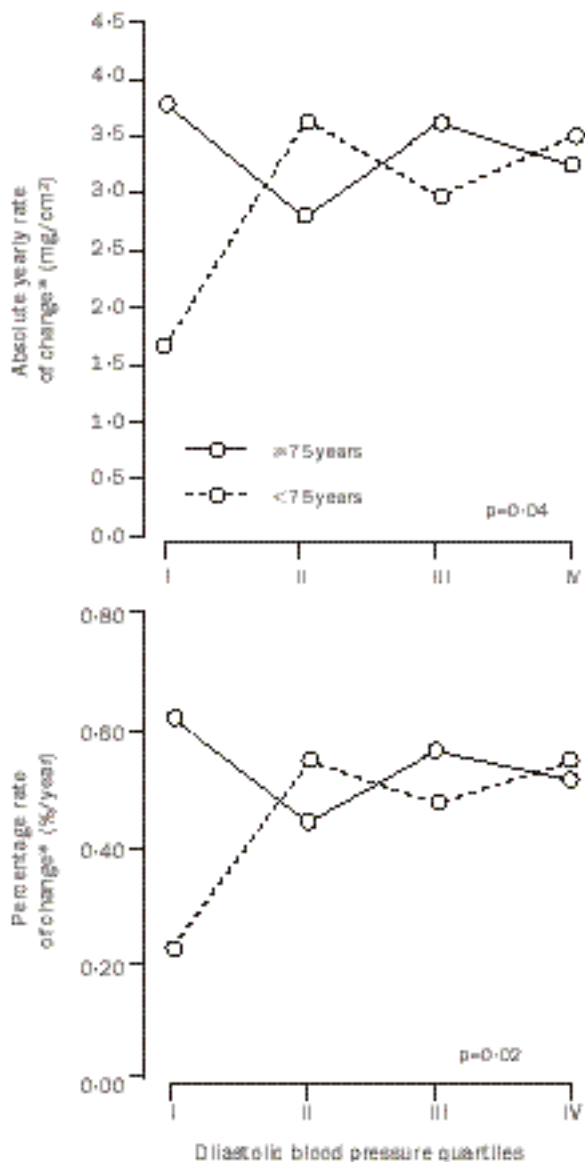
Although the association between systolic blood pressure and bone-mineral loss (absolute and percentage changes) was not modified by age (interactions *p*=0.59 and *p*=0.61), a significant interaction was found with diastolic blood pressure (*p*=0.04 and *p*=0.02; figure). Yearly bone-mineral loss in women younger than 75 years (fully adjusted model, by quartiles) increased from 1.66 mg/cm² (0.52-2.80) to 3.54 mg/cm² (2.58-4.50), equivalent to -0.24% change per year (-0.41 to -0.05) increasing to -0.55% per year (-0.70 to -0.40).

Women who did not complete follow-up were older, had higher blood pressure, and lower femoral-neck bone-mineral density than those who did complete follow-up (table 3). These differences were still present after adjustment for age and bodyweight (data not shown).

Quartiles	Number	Yearly absolute changes (mg/cm ²)		Yearly relative changes (%)	
		Adjusted means (95% CI)	<i>p</i> *	Adjusted means (95% CI)	<i>p</i> *
Systolic blood pressure (mm Hg)					
<124	756	-2.26 (-3.04 to -1.48)		-0.34 (-0.46 to -0.20)	
124-135	1001	-3.45 (-4.11 to -2.79)		-0.53 (-0.63 to -0.43)	
136-147	930	-3.13 (-3.82 to -2.44)		-0.50 (-0.60 to -0.40)	
≥148	989	-3.79 (-4.45 to -3.13)	0.03 (0.01)	-0.59 (-0.69 to -0.49)	0.02 (0.005)
Diastolic blood pressure (mm Hg)					
<70	796	-2.70 (-3.44 to -1.96)		-0.42 (-0.54 to -0.30)	
70-75	948	-3.15 (-3.84 to -2.46)		-0.48 (-0.58 to -0.38)	
76-79	724	-3.36 (-4.14 to -2.58)		-0.53 (-0.65 to -0.41)	
≥80	1198	-3.50 (-4.11 to -2.89)	0.43 (0.10)	-0.55 (-0.65 to -0.45)	0.41 (0.09)

*Expressed as test for heterogeneity (test for linear trend).

Table 2: Yearly absolute and relative rates of change of femoral-neck bone-mineral density during follow-up, adjusted for age, initial bone-mineral density, baseline bodyweight, weight change, smoking, and use of hormone-replacement therapy



Rate of change in femoral-neck bone-mineral density over 3.5 years in women aged 66–91 years not taking thiazides

*Adjusted for age, initial bone-mineral density, bodyweight, weight change, smoking, and use of hormone-replacement therapy.

Discussion

Systolic blood pressure was a significant predictor of bone-mineral loss at the femoral neck. This increased rate of bone loss is not because of differences in age, bodyweight, or weight changes with time, initial bone-mineral density, smoking, or use of hormone-replacement therapy. Furthermore, the effect was not confounded by long-term thiazide diuretic use and persisted after the exclusion of women on other antihypertensive medications at follow-up. However, the size of the effect was notable.

The Study of Osteoporotic Fractures is a continuing longitudinal investigation of elderly white women, which was started in 1986 to study the determinants of bone demineralisation and fractures.^{13–19} During the prospective phases, many measurements have been made at each follow-up assessment. Dual-energy X-ray absorptiometry of the femoral neck was first introduced to the study in 1988–90,¹⁸ and was repeated 3–4 years later.¹⁹ Our analysis is therefore restricted to this site. The study has some limitations. The analysis was restricted to white women, so

Characteristic	Women completing visit 4 (n=3676)	Women not completing visit 4 (n=1883)	p
Age (years)	71 (5)	73 (6)	<0.001
Bodyweight (kg)	65.8 (11.4)	65.5 (12.1)	0.39
Systolic blood pressure (mm Hg)	137 (17)	141 (19)	<0.001
Diastolic blood pressure (mm Hg)	75 (9)	76 (9)	0.05
Femoral-neck bone-mineral density (g/cm ²)	0.646 (0.106)	0.625 (0.112)	<0.001

Values are means (SD).

Table 3: Baseline characteristics of women lost to follow-up and those who attended follow-up

our findings are not generalisable to men or women of other ethnic origins. We also restricted our analysis to the neck of femur, so we cannot conclude about this association at different sites.

Our results were significant and were not affected by restrictions and exclusions, and were unlikely to have been due to chance. Selection bias is also unlikely. Follow-up rates in the Study of Osteoporotic Fracture were high (77% of survivors for this analysis). The women who did not complete follow-up were older, had higher blood pressures, and lower baseline femoral bone-mineral density than those who did complete follow-up. The effect of their loss to follow-up would have led to an exclusion of women with higher blood pressure and lower bone mass, thereby making the association harder to find. We also considered potential confounders. Because of the protective effect of long-term use of thiazide diuretics on bone-mineral density,^{21,22} we restricted our analysis to women who had never used thiazides. Furthermore, exclusion of women on other antihypertensive therapies did not affect our finding of an association between bone-mineral loss and high blood pressure. Differential survival is an unlikely explanation. Women who rapidly lost bone mass and hypertensive women would be less likely to survive, and therefore an association would be harder to detect. Factors that may have an effect on bone-mineral mass and blood pressure (age, weight, smoking, hormone-replacement therapy) were also considered in the multivariate model and did not explain the results. In particular, blood pressure (particularly systolic) and bone-mineral losses increase with age. We adjusted for age in our analysis so that the results are independent of the effect of age. Our results are also consistent with the inverse association between bone-mineral density, stroke incidence,¹⁶ and cardiovascular mortality.²³ We found a significant interaction with age in the relation between diastolic (but not systolic) blood pressure and bone-mineral loss. The positive relation was found only in women younger than 75 years. This finding is intriguing, since the relation between diastolic blood pressure and age becomes less in the very elderly. The lack of association with bone-mineral loss suggests that the pathophysiological mechanism may not operate when diastolic blood pressure falls with age.

High blood pressure is associated with abnormalities in calcium metabolism, including an increase in urinary calcium excretion for a given sodium intake,^{9,10} and evidence of secondary increase in parathyroid gland activity.^{1,2} Hypercalciuria in hypertension has been consistently reported in case-control and cross-sectional studies,⁹ although the underlying mechanism has not been elucidated. This increased urinary calcium loss as a function of blood pressure has been seen in animals with hypertension,^{11,12,24} in normotensive children in the upper part of the distribution for their age,^{8,25} and in

normotensive children of hypertensive adults.^{25,26} Moreover, in hypertensive rats, hypercalciuria is associated with a lowered bone-mineral content.^{11,12} Sustained hypercalciuria in people with high blood pressure leads to an increased risk of bone-mineral loss. Cross-sectional studies have shown a significant negative association between blood pressure and bone-mineral density.^{27,28} Our study established the temporal sequence of such a relation. However, since no urinary calcium measurements were available in our cohort, the mechanism remains speculative. Furthermore, it would be important to investigate whether more bone loss in women with higher blood pressure is associated with increased susceptibility to fractures.

Osteoporosis is the main cause of bone fractures in postmenopausal women and the elderly, and has associated pain, deformity, and loss of independence.²⁹ About 1.5 million fractures per year occur in the USA at an estimated cost of US\$10 billion per year, and just under 100 000 fractures per year occur in the UK at an estimated cost of more than £600 million per year. Fractures are also an important part of the workload of the hospital service. In England, in 1985, there were an estimated 180 000 admissions for treatment of fractures.³⁰ Because of the increasing numbers of elderly people and the increase in the prevalence of osteoporosis, the need for focused preventive strategies has become a public-health priority. Several modifiable risk factors are known (smoking, lack of oestrogens, physical inactivity).³¹ A decrease in the rate of loss of bone-mineral density is achieved with thiazide diuretics,^{21,22} leading to a significant decline in hip fractures.³² Peak bone mass attained in the first 20 years of life and the rate at which bone is lost in later years are the most important factors that influence the occurrence of osteoporosis. Osteoporosis and ensuing fractures are therefore preventable at the population level.³¹ High salt intake has been associated with reduced peak bone mass in young girls aged 8–13 years³³ and a higher rate of bone-mineral loss in postmenopausal women.³⁴ High salt intake causes an increase in urinary calcium excretion¹⁰ and decrease in dietary intake should promote a positive calcium balance and lower blood pressure. Decreased salt intake should therefore lessen the risk of osteoporosis and hip fractures in elderly people and also have a blood-pressure-lowering effect.³⁵

Contributors

Francesco Cappuccio and Elaine Meilahn developed the idea for the study. Francesco Cappuccio and Jane Cauley designed the analysis. Joseph Zmuda did the statistical analysis. Jane Cauley is one of the five principal investigators of the Study of Osteoporotic Fractures Research Group. Francesco Cappuccio drafted the manuscript and all investigators contributed to its revision and approved the final version.

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Association of mis-sense substitution in *SRD5A2* gene with prostate cancer in African-American and Hispanic men in Los Angeles, USA

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Summary

Background Prostate cancer is a very common disease in more-developed countries, but its cause is largely unknown. It is an androgen-dependent cancer, and androgens have been proposed as having a substantial role in predisposition to the disease. Thus, variations in androgen metabolism genes may affect risk of this disease.

Methods We screened 216 African-American and 172 Hispanic men with prostate cancer, and 261 African-American and 200 Hispanic healthy men (controls), from a large prospective cohort study (the Hawaii-Los Angeles Multiethnic Cohort Study) for a mis-sense substitution in the human prostatic (or type II) steroid 5 α -reductase (*SRD5A2*) gene, the product of which controls metabolic activation of testosterone to dihydrotestosterone. This mis-sense substitution results in an alanine residue at codon 49 being replaced with threonine (A49T). We also reconstructed this mutation in the *SRD5A2* cDNA, and overexpressed the enzyme in mammalian tissue culture cells.

Findings The A49T aminoacid substitution in the *SRD5A2* gene increased the risk of clinically significant disease 7.2-fold in African-American men (95% CI=2.17–27.91; p=0.001) and 3.6-fold in Hispanic men (1.09–12.27; p=0.04). The mutant enzyme had a higher in-vitro V_{max} than the normal enzyme (9.9 vs 1.9 nmol min⁻¹ mg⁻¹).

Interpretation The A49T variant of the *SRD5A2* gene may be a significant contributor to the incidence of prostate cancer

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in African-American and Hispanic men in Los Angeles. We estimate that the population attributable risk due to this aminoacid substitution for clinically significant disease is about 8% in both populations. Increased conversion of testosterone to dihydrotestosterone catalysed by this variant steroid 5 α -reductase enzyme may be the cause of the increased risk.

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Introduction

Prostate cancer is a very common disease in more-developed countries: more than 39 200 men died of the disease in the USA in 1998,¹ and 50 122 died in the European Union in 1990.² Prostate cancer is androgen dependent,^{3,4} and we have previously proposed that variations in androgen metabolism may affect a man's risk of this disease.^{4–6} We have provided evidence that increased intraprostatic androgen metabolism, particularly through the enzyme steroid 5 α -reductase, may have an important role in predisposition to prostate cancer. This enzyme catalyses the conversion of testosterone to dihydrotestosterone—the most potent androgen in the prostate. Thus, genetic variants encoded by the steroid 5 α -reductase gene (*SRD5A2*) may have an effect on predisposition to prostate cancer. We report our epidemiological and biochemical findings on the relation between prostate cancer and a constitutional (germline) mis-sense substitution in *SRD5A2*, which results in the replacement of an alanine residue at codon 49 with threonine (A49T).⁷ This substitution is associated with a significantly increased risk of prostate cancer (particularly of an advanced nature), probably through increased metabolic activation of testosterone to dihydrotestosterone.

Methods

Epidemiology

This case-control study was part of the prospective Hawaii-Los Angeles Multiethnic Cohort Study of Diet and Cancer, which has been described in detail elsewhere.⁸ About 200 000 African-