Effects of low dose versus conventional dose thiazide diuretic on insulin action in essential hypertension

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Abstract

Objective—To see whether low dose thiazide diuretics given to patients with essential hypertension might avoid the adverse metabolic consequences seen with conventional doses.

Design—Double blind randomised crossover study of two 12 week treatment periods with either low dose (1.25 mg) or conventional dose (5.0 mg) bendrofluazide given after a six week placebo run in period.

Setting—Outpatient clinics serving the greater Belfast area.

Subjects—16 white non-diabetic patients (9 male) under 65 with essential hypertension recruited from general practices within the greater Belfast area.

Main outcome measures—Systolic and diastolic blood pressure and peripheral and hepatic insulin action.

Results—One man failed to complete the study. There were no differences between doses in their effects on systolic and diastolic blood pressure. Bendrofluazide 1.25 mg had substantially less effect on serum potassium concentration than the 5.0 mg dose. There were no intertreatment differences in fasting glucose, insulin, cholesterol, and triglyceride concentrations. Bendrofluazide 5.0 mg significantly increased postabsorptive endogenous glucose production compared with baseline (mean 10.9 (SD 1.2) v 10.0 (0.8) $\mu\text{mol/kg/min}$), whereas bendrofluazide 1.25 mg did not. Postabsorptive endogenous glucose production was significantly higher with bendrofluazide 5.0 mg compared with 1.25 mg (10.9 (1.2) v 9.9 (0.8) $\mu\text{mol/kg/min}$) but was suppressed to a similar extent after insulin (bendrofluazide 5.0 mg 2.8 (1.5) $\mu\text{mol/kg/min}$ v bendrofluazide 1.25 mg 2.2 (1.5) $\mu\text{mol/kg/min}$). Exogenous glucose infusion rates required to maintain euglycaemia were not significantly different between doses and were similar to baseline.

Conclusions—Bendrofluazide 1.25 mg is as effective as conventional doses but has less adverse metabolic effect. In contrast with conventional doses, low dose bendrofluazide has no effect on hepatic insulin action. There is no difference between low and conventional doses of bendrofluazide in their effect on peripheral insulin sensitivity.

Introduction

Thiazide diuretics were introduced into clinical practice in 1957.¹ Since then they have remained popular for arterial hypertension, providing an effective, well tolerated once daily treatment. They have been used in many large prospective clinical trials in mild hypertension, producing consistent benefit, particularly in reducing the excess risk of stroke.^{2,4}

However, thiazide diuretics are associated with several potentially deleterious metabolic effects.^{5,6} These include hypokalaemia, hyperuricaemia, short term hyperlipidaemia, impaired glucose tolerance, and an increased risk of diabetes. It has been proposed that these potentially detrimental effects may to some extent offset the benefit gained by blood pressure

reduction.⁷ But many of these adverse effects are dose dependent and can be minimised by using lower doses. The effectiveness of low dose thiazide diuretics in the absence of adverse metabolic effects has been emphasised for bendrofluazide,⁸ cyclopenthiazide,⁹ and hydrochlorothiazide.¹⁰

There are multiple risk factors for coronary artery disease in patients with hypertension before they receive any drug treatment.¹¹⁻¹³ Comparatively minor degrees of glucose intolerance comparable to those in many patients with hypertension significantly increase the risk of coronary artery disease.¹⁴ Abnormalities of lipoprotein metabolism have also been described in patients with untreated hypertension.¹³ Hyperinsulinaemia is common in hypertension,^{11,15} and it also may be a risk factor for coronary artery disease.¹⁶ Finding impaired insulin action in essential hypertension before treatment¹⁷ has led to suggestions that insulin resistance is an underlying metabolic defect in hypertension. Not only would this contribute to the rise in arterial blood pressure but it would also account for the range of observed abnormalities in carbohydrate, lipid, and lipoprotein metabolism so prevalent in hypertensive subjects.¹¹

Pollare *et al* found that hydrochlorothiazide in conventional dosage seemed to decrease insulin mediated glucose disposal.¹⁸ Given this and the evidence promoting insulin resistance as a vascular risk factor, it has been argued that those antihypertensive drugs which improve insulin action should be used in preference to drugs such as thiazide diuretics which may adversely affect insulin sensitivity.

No information is available regarding the effects of low dose thiazide diuretics on insulin action. Furthermore, we know of only one study in which hepatic insulin sensitivity was assessed during thiazide treatment; that study used a conventional dose of cyclopenthiazide.¹⁹ We have examined the effects of 1.25 mg and 5.0 mg bendrofluazide on insulin action in non-diabetic hypertensive subjects in a double blind randomised crossover study. We used the glucose clamp technique in conjunction with isotope dilution methodology to provide a detailed analysis of peripheral and hepatic insulin action.

Subjects and methods

Patients aged under 65 with essential hypertension, either newly diagnosed or receiving treatment with a single agent, were recruited from general practices within the greater Belfast area. All were of white west European origin. Patients were excluded if they weighed greater than 125% of ideal (Metropolitan Life Insurance tables, 1955) or had significant cardiac, hepatic, or renal disease or a history of gout or were receiving non-steroidal anti-inflammatory agents or corticosteroids. Patients with secondary hypertension were excluded, as were those whose diastolic blood pressure was outside the range 95-110 mm Hg after a placebo run in period of six weeks. All patients gave written informed consent, and the protocol was approved by the ethics committee of The Queen's University of Belfast.

A randomised double blind crossover design was

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BMJ 1994;309:226-30

used. All antihypertensive agents were withdrawn and placebo substituted for six weeks. Patients were seen every two weeks, and at the end of the placebo period those with a diastolic blood pressure greater than 95 mm Hg were eligible to continue.

Patients were randomised by using random numbers to receive either 1.25 mg or 5.0 mg bendrofluazide as a single daily dose for 12 weeks. Randomisation was designed to ensure that numbers receiving each treatment during the first phase were about equal. During this period patients were reviewed every four weeks. When 12 weeks had elapsed patients were switched to placebo for a further six weeks, after which they received the other dose of bendrofluazide for 12 weeks. Patients were assessed after four and six weeks of this second placebo period and at four week intervals during the second treatment period. All medication was supplied by Boots Pharmaceuticals, Nottingham. Placebo and active tablets were identical in taste and appearance. Patients were asked to bring the study medication with them at each visit to check on compliance.

ASSESSMENT

Throughout the trial patients were seen by the same investigator. Patients attended fasting and had their blood pressure measured in the same arm at the same time of day after resting supine for 10 minutes. Blood pressure was measured with a Hawksley random zero sphygmomanometer with the arm supported at heart level. Arterial pressure was measured to the nearest 2 mm Hg. Diastolic blood pressure was read at the point of disappearance of the Korotkoff sounds (phase V). The mean of three readings was used. At each visit heart rate and weight were measured and, avoiding forearm exercise, venous blood was withdrawn for measurements of plasma glucose, serum urea, urate, and electrolytes, glycated haemoglobin, haemoglobin, and lipid concentrations.

Insulin action was assessed at the end of the run in period and at the end of the two active treatment periods by using the euglycaemic glucose clamp technique.^{20,21} Patients were admitted to the metabolic unit at 7.45 am on the morning of the study after a 12 hour overnight fast. An antecubital vein was cannulated (18 gauge; Venflon Viggo, Helsingborg, Sweden) and used for all infusions. A dorsal hand vein on the opposite side was cannulated (21 gauge; Venflon Viggo) and the hand placed in a temperature controlled plexiglass box (Northern Ireland Technology Centre, Automation Division, Queen's University of Belfast) maintained at 55°C to allow intermittent sampling of arterialised venous blood.

A primed continuous infusion of high performance liquid chromatography purified [6-³H]glucose (New England Nuclear Research Products Division, Dupont Ltd, Stevenage, United Kingdom (NET 100C)) was given during a two hour equilibration period (–120 minutes to zero time), after which a two hour continuous infusion of insulin (Humulin S; Eli Lilly and Co, Basingstoke) was begun at 1 mU/kg/min. Plasma glucose was maintained at the fasting concentration by an exogenous glucose infusion (20%). Exogenous glucose was prelabelled with [6-³H] glucose to match the predicted basal plasma glucose specific activity as described²² with the modification that the primed continuous tracer infusion was reduced to 50% of the basal rate after 20 minutes and to 25% of basal after 40 minutes (in order to maintain tracer steady state) and was maintained at this rate throughout the remainder of the hyperinsulinaemic period.

ANALYTICAL TECHNIQUES

Arterialised venous blood was used for all analyses. Plasma for measurement of glucose specific activity

was deproteinised with barium dihydroxide and zinc sulphate by the method of Somogyi.²³ After centrifugation the supernatant was passed sequentially through anion (AG1-X8; BioRad Laboratories, Watford) and cation (AG50W-X8; BioRad) exchange columns to remove charged molecules. Samples were counted in a liquid scintillation spectrometer (Tri-Carb 2000 CA, Canberra Packard, Pangbourne). Aliquots of tracer infusate and labelled exogenous glucose infusion were spiked into non-radioactive plasma and processed in parallel with plasma samples to allow calculation of [6-³H]glucose infusion rates.

Serum insulin concentration was measured by radioimmunoassay with insulin antibody precipitate.²⁴ Commercially available reagent kits were used to measure serum free fatty acid (Wako Chemicals, Neuss, Germany), β -hydroxybutyrate (Randox Laboratories, Crumlin), and serum glycerol (Randox Laboratories) concentrations.

CALCULATIONS

The non-steady state equations of Steele *et al*²⁵ as modified by De Bodo *et al*²⁶ were used to determine rates of glucose appearance and disappearance during the periods –30 minutes to zero time and 90 to 120 minutes, assuming a pool fraction value of 0.65 and an extracellular volume of 190 ml/kg. Infusion rates of [6-³H] glucose were calculated as the sum of the tracer infused continuously and the tracer in the labelled exogenous glucose infusion. Rates of endogenous (hepatic) glucose production were then calculated by subtraction of the exogenous glucose infusion rates required to maintain euglycaemia from the isotopically determined rates of glucose appearance.

STATISTICAL METHODS

The power of the study, calculated from previous clamp data,¹⁹ gave a 90% chance of detecting a 10% change in insulin action at the 5% level of significance. Blood pressure and biochemical values at the end of each period of placebo or active treatment were used for statistical analysis. Statistical analysis was as recommended by Hills and Armitage.²⁷ This method enables comparison of low and conventional dose bendrofluazide to be adjusted for any period effects. The method also supplies a test for treatment period interaction. Comparison of doses was derived from the differences in responses between the two periods. Significance was assessed with a *t* statistic. No carryover effect was detected for any variable measured and there was therefore no necessity to analyse any variables as a parallel study. Results are presented as means and standard deviation (SD), except where stated otherwise. Significance was taken as $P < 0.05$.

Results

Of 20 patients enlisted for the study, 16 fulfilled the entry criteria. Fifteen patients (eight male; mean age 54 (SD 8) years; body mass index (weight (kg)/height (m)²) 27.2 (3.1)) completed the full protocol. At the end of the placebo run in period patients had a mean blood pressure of 163 (15)/105 (4) mm Hg. Of the four patients who were withdrawn before the first active treatment period, three had a diastolic blood pressure less than 95 mm Hg at the end of the placebo run in phase and one withdrew during the placebo phase. One patient was withdrawn during the study because of clinical gout (serum urate concentration 0.63 mmol/l). This patient was taking bendrofluazide 5.0 mg.

Patient compliance was good, over 95% of the tablets being taken by all participants. The effects of each dose of bendrofluazide on systolic and diastolic blood pressure are shown in table I. The 1.25 mg and 5.0 mg doses of bendrofluazide produced significant decreases

in systolic and diastolic blood pressure after 12 weeks. There were no statistically significant differences between the two doses after 12 weeks. Neither heart rate nor body weight changed after either dose of bendrofluazide.

The effects of treatment on various biochemical variables are shown in table II. Bendrofluazide 5.0 mg produced a greater reduction in serum potassium concentration (0.5 (0.2) mmol/l) than bendrofluazide 1.25 mg (0.1 (0.2) mmol/l; $P < 0.01$). In no case did the serum potassium concentration fall below 3.4 mmol/l. No significant changes in fasting glucose or glycated haemoglobin concentrations were noted with either dose of bendrofluazide. There were no significant changes in total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, or total triglyceride concentrations with either treatment, nor were there any significant differences between treatments.

Results from the euglycaemic glucose clamp studies are summarised in table III. Fasting arterialised venous plasma glucose concentrations were unchanged by treatment. Fasting serum insulin concentration was significantly increased after 12 weeks' treatment with bendrofluazide 5.0 mg ($P < 0.05$) but not with 1.25 mg. Plasma glucose concentrations during the clamp studies were similar, with mean coefficients of variation less than 3.7%. Insulin infusion of 1 mU/kg/min led to comparable concentrations of steady state plasma insulin. Exogenous glucose infusion rates required to maintain euglycaemia during the last 30 minutes of the glucose clamp (an index of peripheral insulin sensitivity) were not significantly different between doses and were similar to baseline.

TABLE I—Effect of low dose (1.25 mg) and conventional dose (5.0 mg) bendrofluazide on systolic and diastolic blood pressure. Values are means (SD)

	Bendrofluazide Dose	Week			
		0	4	8	12
Systolic blood pressure (mm Hg)	1.25 mg	162 (15)	153 (12)*†	150 (12)*†	145 (15)***
	5.0 mg	163 (15)	147 (12)***	143 (12)***	140 (12)***
Diastolic blood pressure (mm Hg)	1.25 mg	105 (4)	98 (8)**	98 (8)**	95 (8)***
	5.0 mg	105 (8)	99 (8)**	95 (8)**	92 (8)***

* $P < 0.005$ v baseline (week 0); ** $P < 0.001$ v baseline; *** $P < 0.0001$ v baseline. † $P < 0.05$, 1.25 mg v 5.0 mg.

TABLE II—Effect of low dose (1.25 mg) and conventional dose (5.0 mg) bendrofluazide on circulating electrolyte, glycated haemoglobin, urate, glucose, and lipid concentrations. Values are means (SD)

	Bendrofluazide 1.25 mg		Bendrofluazide 5.0 mg	
	Week 0	Week 12	Week 0	Week 12
Sodium (mmol/l)	141 (2)	140 (2)	140 (2)	140 (4)
Potassium (mmol/l)	4.3 (0.4)	4.2 (0.4)	4.2 (0.4)	3.7 (0.4)*†
Urea (mmol/l)	5.4 (1.2)	5.6 (1.5)	5.4 (1.2)	5.7 (1.2)
Creatinine (μmol/l)	88 (12)	90 (12)	88 (12)	90 (15)
Urate (mmol/l)	0.35 (0.08)	0.37 (0.08)	0.36 (0.08)	0.40 (0.08)
Fasting glucose (mmol/l)	5.1 (0.8)	5.2 (1.2)	4.8 (0.8)	5.2 (1.2)
Haemoglobin A _{1c} (%)	3.7 (0.8)	3.7 (0.8)	3.6 (0.8)	3.7 (0.8)
Cholesterol (mmol/l)	5.74 (0.97)	5.74 (0.81)	5.69 (0.93)	5.93 (1.01)
Low density lipoprotein cholesterol (mmol/l)	3.95 (0.81)	3.82 (0.70)	3.81 (0.81)	3.95 (0.97)
High density lipoprotein cholesterol (mmol/l)	1.23 (0.27)	1.24 (0.27)	1.23 (0.23)	1.25 (0.27)
Triglycerides (mmol/l)	1.61 (0.81)	1.80 (0.85)	1.75 (0.81)	1.95 (0.97)

* $P < 0.01$ v baseline (week 0). † $P < 0.01$, 1.25 mg v 5.0 mg.

TABLE III—Results summary for euglycaemic glucose clamps at baseline and after 12 weeks' treatment with low dose (1.25 mg) and conventional dose (5.0 mg) bendrofluazide. Values are means (SD)

	Baseline (week 0)	1.25 mg (week 12)	5.0 mg (week 12)
Fasting glucose (mmol/l)	5.3 (0.4)	5.4 (0.4)	5.5 (0.4)
Mean clamp glucose (mmol/l)	5.2 (0.4)	5.2 (0.4)	5.2 (0.4)
Fasting serum insulin (mU/l)	7.0 (2.7)	7.3 (3.9)	8.5 (3.1)*
Steady state clamp insulin (mU/l)	86 (10)	78 (12)	82 (11)
Exogenous glucose infusion rate (90–120 min; μmol/kg/min)	22.9 (7.3)	23.1 (7.3)	21.5 (7.3)
Postabsorptive endogenous glucose production (μmol/kg/min)	10.0 (0.8)	9.9 (0.8)†	10.9 (1.2)*†
Endogenous glucose production during clamp (90–120 min; μmol/kg/min)	1.8 (1.2)	2.2 (1.5)	2.8 (1.5)
Glucose disappearance rate (90–120 min; μmol/kg/min)	25.4 (7.0)	25.2 (6.6)	25.2 (7.0)

* $P < 0.05$ v baseline. † $P < 0.05$, 1.25 mg v 5.0 mg.

Change in serum non-esterified fatty acid, β hydroxybutyrate, and glycerol concentrations during clamp studies. Data are expressed as means and 95% confidence intervals (bars)

Postabsorptive endogenous glucose production (an index of hepatic insulin sensitivity) increased significantly compared with baseline after treatment with 5.0 mg bendrofluazide whereas 1.25 mg had no such effect (table III). Endogenous glucose production was significantly higher after 5 mg compared with 1.25 mg. After insulin endogenous glucose production was suppressed to a similar extent with both doses. Total glucose disappearance rates during the 1.0 mU/kg/min insulin infusion were not significantly different between doses.

Postabsorptive concentrations of serum non-esterified fatty acids, β-hydroxybutyrate, and glycerol were unchanged by treatment with either dose. During hyperinsulinaemia rapid suppression to a similar extent was seen with both doses (figure).

Discussion

Thiazide diuretics remain one of the most popular treatments for raised arterial blood pressure despite reports of their adverse effects on electrolyte, glucose, and lipid metabolism. If we are to continue to use them we must minimise adverse metabolic effects, and one way to do this is to use lower doses.

In this study reduction of blood pressure was similar after treatment with both low and conventional dose bendrofluazide. The magnitude of the anti-hypertensive effect after low dose bendrofluazide (17/10 mm Hg) was comparable to that reported in a much larger, parallel group study (13/10 mm Hg).⁸ Furthermore, we found low dose bendrofluazide to have no detrimental effects on peripheral or hepatic insulin action. By contrast, conventional dose bendrofluazide produces hepatic insulin resistance, as evidenced by hyperinsulinaemia and increased basal endogenous glucose production.

Thiazide diuretics in high dosage impair glucose tolerance and in some cases precipitate overt diabetes

mellitus.^{28,29} These effects may be dose dependent.¹⁰ Several mechanisms, including hypokalaemia³⁰ and reduced insulin secretion,³¹ have been proposed to explain the impaired carbohydrate metabolism during thiazide treatment. Finding peripheral insulin resistance in essential hypertension before drug treatment¹⁷ has concentrated interest on the effects of various classes of antihypertensive agents on insulin sensitivity. An early report suggested that chlorothiazide interferes with the peripheral utilisation of glucose.³² Much later Pollare *et al*, using the euglycaemic glucose clamp technique, found that hydrochlorothiazide 40 mg daily causes an 11% reduction in insulin mediated glucose disposal.¹⁸

In this study our hypertensive patients were insulin resistant at baseline compared with normal subjects studied previously.¹⁹ Low dose bendrofluazide (1.25 mg) produced no change in peripheral insulin action compared with baseline. Though no differences between doses were observed, 5.0 mg bendrofluazide produced a 6% reduction in insulin mediated glucose disposal. This did not reach significance ($P=0.1$) and was in contrast with the findings of Pollare *et al* with an equivalent conventional dose. The possibility of a type II error exists in that the power of our study was sufficient to detect differences of around 10% at the 5% level of significance. Alternatively, effects on peripheral insulin action may vary with different thiazide diuretics. We have found that insulin mediated glucose disposal does not change after 12 weeks' treatment with cyclopentiazide 500 µg.¹⁹ What appears very clear from this study, however, is that a lower than conventional dose of bendrofluazide does not worsen the peripheral insulin resistance of patients with essential hypertension.

Whereas patients with essential hypertension have significant peripheral insulin resistance, hepatic insulin sensitivity seems to be largely preserved.^{17,19} Most studies of the effects of antihypertensive agents on insulin sensitivity have concentrated on peripheral insulin action, so that little information is available on effects on hepatic insulin sensitivity. We have detected a small but significant increase in basal endogenous (hepatic) glucose production (9%) with the use of conventional dose bendrofluazide. As basal insulin concentrations were also increased, this may represent induction of a degree of hepatic insulin resistance even though suppression of endogenous glucose production was not affected. We have noted a similar effect with the use of conventional doses of cyclopentiazide.¹⁹ Insulin induced suppression of lipolysis (as reflected in the suppression of non-esterified free fatty acids during hyperinsulinaemia) was not impaired by bendrofluazide 5 mg, indicating that hepatic insulin resistance does not extend to effects on lipid metabolism.

Significant hepatic resistance to insulin is a characteristic defect in glucose metabolism in non-insulin dependent diabetes mellitus, leading to increased hepatic glucose production both in the fasting state (roughly 20-25% with moderate hyperglycaemia) and after meals.³³⁻³⁵ Increased hepatic glucose production may be an early and fundamental defect in non-insulin dependent diabetes.³⁶ The increase in hepatic glucose production with conventional dose thiazide diuretics could therefore be related to the increased incidence of impaired glucose intolerance and subsequent development of diabetes in patients with hypertension treated with these agents. However, it is clear from our study that with the use of low doses of bendrofluazide the deterioration in hepatic insulin action seen with more conventional doses is avoided.

A differential effect between doses was evident for serum potassium concentration. The dose-response nature of thiazide effects on serum potassium has been described.⁸⁻¹⁰ Many studies have shown that thiazide

Clinical implications

- Insulin resistance may be important in the pathogenesis and clinical course of essential hypertension
- In conventional doses thiazide diuretics impair glucose tolerance, worsen insulin resistance, and increase the risk of diabetes
- Evidence now shows that low dose bendrofluazide is as effective as a more conventional dose in reducing blood pressure in hypertensive patients and does not have adverse metabolic effects
- Whereas low dose bendrofluazide has no detrimental effects on insulin action, conventional dose bendrofluazide induces hypokalaemia and impairs hepatic insulin action
- The lowest possible doses of thiazide diuretics should be used

diuretics adversely affect lipid values and lipoprotein profiles, at least in the short term.^{37,38} However, this was found with comparatively high doses of thiazides. Lower doses, as used in this study, seem to avoid effects on lipid concentrations.

In conclusion we have shown the effectiveness of bendrofluazide 1.25 mg daily in mild hypertension. Compared with a more conventional dose, low dose bendrofluazide produced no adverse metabolic effects and in particular no deleterious effects on either peripheral or hepatic insulin action. In contrast, the use of bendrofluazide at a more conventional dose of 5.0 mg daily produced hypokalaemia and impaired hepatic insulin action. This second effect may have profound importance in the subsequent development of impaired glucose tolerance and non-insulin dependent diabetes in hypertensive patients treated with conventional dose thiazide diuretics. However, the use of 1.25 mg bendrofluazide may successfully decrease blood pressure with minimal upset to the metabolic profile.

We are grateful to Dr C Patterson, department of community medicine and medical statistics, The Queen's University of Belfast, for statistical advice. We also thank Mr Noel Bell for the metabolite assays. During these studies Dr R Harper was a Royal Victoria Hospital research fellow.

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(Accepted 27 April 1994)

Exercise, smoking, and calcium intake during adolescence and early adulthood as determinants of peak bone mass

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Abstract

Objective—To evaluate the contribution to peak bone mass of exercise, smoking, and calcium intake in adolescents and young adults.

Design—Prospective cohort study with end point measurement (bone mineral density) after 11 years' follow up for lifestyle.

Setting—Five university hospital clinics.

Subjects—264 (153 females, 111 males) subjects aged 9 to 18 years at the beginning of the follow up and 20 to 29 years at the time of measurement of bone mineral density.

Main outcome measure—Bone mineral density of lumbar spine and femoral neck by dual energy x ray absorptiometry; measures of physical activity and smoking and estimates of calcium intake repeated three times during follow up.

Results—In the groups with the lowest and highest levels of exercise the femoral bone mineral densities (adjusted for age and weight) were 0.918 and 0.988 g/cm² for women (P=0.015, analysis of covariance) and 0.943 and 1.042 g/cm² for men (P=0.005), respectively; at the lumbar spine the respective values were 1.045 and 1.131 (P=0.005) for men. In men the femoral bone mineral densities (adjusted for age, weight, and exercise) were 1.022 and 0.923 g/cm² for the groups with the lowest and highest values of smoking index (P=0.054, analysis of covariance). In women the adjusted femoral bone mineral density increased by 4.7% together with increasing calcium intake (P=0.089, analysis of covariance). In multiple regression analysis on bone mineral density of the femoral neck, weight, exercise, age, and smoking were independent predictors for men; with weight, exercise, and age for women. These predictors together explained 38% of the variance in bone mineral density in

women and 46% in men. At the lumbar spine, weight, smoking, and exercise were predictors for men; and only weight for women.

Conclusions—Regular exercise and not smoking is important in achieving maximal peak bone mass in adolescents and young adults.

Introduction

Peak bone mass in young adults is a major determinant of bone mass later in life.¹ Thus even though most osteoporotic fractures occur in elderly people, the risk of osteoporosis may be profoundly affected by events in early life. Genetic factors play a major part in the determination of peak bone mass, accounting for up to 80% of the variance,² but 20% or more may be due to environmental factors, including exercise, smoking, and calcium intake.

The role of these lifestyle factors in adolescents and young adults as determinants of peak bone mass has, however, been examined in only a few studies,³⁻¹⁰ and environmental factors during youth were estimated by retrospective surveys,³⁻⁷ an extremely crude method of assessment. Furthermore, bone mineral content or density was usually measured only at radial or vertebral sites^{3,4,6-8} and not at the femoral sites, which are most important with regard to osteoporotic hip fractures later in life. To date, the role of calcium intake in achieving peak bone mass has been most convincingly supported by prospective interventional studies^{8,10} and that of exercise in a cross sectional study of children aged 5-14.⁹ The effect of smoking has not been studied in these age groups.

The cardiovascular risk in young Finns study was originally designed to obtain information on risk factors for coronary heart disease and their determinants in childhood. The study began in 1980 with

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