Do antihypertensive drugs precipitate diabetes in predisposed men?

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Abstract

Objective—To evaluate the influence of antihypertensive treatment and metabolic characteristics on the development of diabetes mellitus in middle aged men.

Design—Prospective study over an average of nine years.

Setting—Community based health survey of middle aged men carried out at the University of Uppsala.

Subjects—Seventy three hypertensive men aged 49-54 and 65 normotensive controls matched for body mass index, glucose disappearance rate (k value) at an intravenous glucose tolerance test, and serum triglyceride and cholesterol concentrations.

Interventions—Hypertensive group was treated with β blockers, thiazides, hydralazine, or combinations of these drugs. Treatment was not randomised.

Measurements and main results—Intravenous glucose tolerance, fasting blood glucose and serum lipid and insulin concentrations, body weight and height, three skinfold measurements, and blood pressure were recorded both during an initial health screening survey in 1970-3 and at a follow up survey in 1980-3. In the period between the two surveys 12 hypertensive men and two controls developed diabetes. Review of values obtained at the initial survey showed that the hypertensive men who developed diabetes or impaired glucose tolerance could be distinguished from those hypertensive men who did not by virtue of a higher fasting serum insulin concentration (26.1 v 15.2 mU/l (confidence interval of difference -15.2 to -6.2)), a lower peak serum insulin concentration (78.9 v 94.3 mU/l (confidence interval of difference -1.1 to 41.1)), and a lower k value (1.29 v 1.68 (confidence interval of difference -0.02 to 0.68)). The insulin index (peak insulin concentration divided by fasting insulin concentration), however, decreased significantly in the hypertensive men over time irrespective of whether they developed diabetes but did not change in the controls. Furthermore, the serum triglyceride concentration increased in the treated group and decreased in the controls.

Conclusion—A severalfold difference in the incidence of diabetes between treated hypertensive and non-treated, normotensive men may be a consequence of the treatment, which may be particularly deleterious in men predisposed to diabetes.

Introduction

Numerous reports have expressed concern about the metabolic effects of antihypertensive drugs.¹⁻¹¹ There has been suspicion that several of the first line drugs may derange lipid metabolism or precipitate diabetes. We describe changes in carbohydrate metabolism and serum lipoprotein concentrations in hypertensive men after almost 10 years of treatment compared with a matched non-hypertensive control group. Our intention was to evaluate the degree of impairment of glucose tolerance (and the development of diabetes mellitus) in the two groups, who were metabolically similar at the start of the study. The hypertensive men received drug treatment throughout, whereas the

controls were normotensive at the start and not taking drugs at follow up.

Subjects and methods

The hypertensive and control groups were derived from a larger cohort of men who were participating in a health survey and who were examined in 1970-3 and again in 1980-3.

HYPERTENSIVE GROUP

The initial health survey was conducted among 2322 men born in 1920-4 and who therefore were aged 50 at the time of first examination.¹² Of the 174 men identified who had primary hypertension (figure), 87 were newly diagnosed cases (untreated diastolic pressure ≥ 105 mm Hg on two occasions) and 87 already receiving treatment. Treatment at a special hypertension clinic was offered to all these men, 91 of whom declined because they were attending other physicians. The remaining 83 men accepted and subsequently were checked twice a year for almost a decade.¹³ Three of the hypertensive men were known to be diabetic at the time of the first health survey and had blood glucose concentrations of 6.7 - 9.8 mmol/l.

All men in the first health survey who had serum cholesterol or triglyceride concentrations, or both, above the 80th centile on two occasions were treated for hyperlipidaemia. Twenty three of the hypertensive men were given dietary advice for this reason. Pharmacological treatment of hypertension, however, was given priority over pharmacological treatment of hyperlipidaemia in the hyperlipidaemic hypertensives.

Flow diagram of composition of the two study groups of men

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The second health survey was carried out among all participants who were still living in Uppsala in 1980-3 and who attended for examination. They included 73 of the hypertensive follow up group.

NORMOTENSIVE CONTROLS

Controls were chosen from the non-hypertensive men examined in the initial survey (figure). As hypertensive people are more often obese than their normotensive peers and more commonly have impaired glucose tolerance¹⁴ and hyperlipidaemia, the control group was obtained by matching for body mass index, glucose disappearance rate (*k* value) at an intravenous glucose tolerance test (available in most cases), and serum triglyceride and cholesterol concentrations, these data having been obtained in the initial survey. Three controls were selected by computer for each hypertensive man. They were matched, firstly, for body mass index, then for serum triglyceride and cholesterol concentrations, and, finally, for *k* value from the intravenous glucose tolerance test. The controls were invited to attend in the order in which they were identified by the computer. If one did not attend the second was invited and so on. The matching procedure was performed before the start of the second health survey in 1980.

At the second survey 65 normotensive controls were found to be suitable for the analysis.

PROCEDURES

For both the initial survey and the follow up survey subjects were contacted by letter and invited to attend for examination. They were instructed to fast and refrain from smoking from midnight. No dietary recommendations were given for the days preceding the examination.

Intravenous glucose tolerance tests were performed during both examinations in most hypertensive and control men together with measurements of anthropometric variables, blood pressure, and serum lipid and lipoprotein concentrations. Blood pressure and anthropometric measurements were recorded as far as possible in the same way on the two occasions. Blood pressure was measured on the right arm after 10 minutes' recumbency by using a mercury manometer. Systolic and diastolic pressures were read to the nearest 5 mm Hg, diastolic pressure being recorded at Korotkoff phase V. Fatfold thickness was measured with a calliper¹⁵ on the back of the middle portion of the right upper arm, just below the scapula, and to the right of the umbilicus.

The intravenous glucose tolerance test was performed by the same method in the two surveys. At the first screening examination 1692 of the 2322 participants were tested. Glucose 0.5 g/kg as a 50% solution was given into an antecubital vein over about two and a half minutes. Samples for blood glucose determination were drawn before and 20, 30, 40, 50, and 60 minutes after the start of the injection. The subjects remained supine throughout. Glucose tolerance was expressed as the *k* value, as described.¹⁶

In addition, the fasting blood glucose concentration was measured in all subjects and an oral glucose tolerance test performed at follow up in those with values higher than 5.6 mmol/l. A dose of 75 g glucose in 300 ml water was given and blood samples for glucose assay taken before and 30, 60, 90, and 120 minutes after intake. On the basis of the oral glucose tolerance test the subjects were divided into those with normal or impaired glucose tolerance and those with diabetes mellitus, as defined by the National Diabetes Data Group.¹⁷ In contrast with the recommendation of that group, however, only one oral glucose tolerance test was performed. The classification of diabetes at the first investigation was made in retrospect and thus was

based on a fasting blood glucose concentration (available in all subjects) of ≥ 6.7 mmol/l either alone or in combination with a *k* value of ≤ 0.9 from the intravenous glucose tolerance test, which was performed in 54 of the 73 hypertensive men and 46 of the 65 controls.

LABORATORY METHODS

The method of measuring the blood glucose concentration differed between the two surveys. In the follow up survey glucose was measured with a glucose oxidase method (Boehringer-Mannheim) on an LKB 7400 photometer. As the mean glucose concentrations had been higher in the original survey, a correction factor of 0.92 was used.

Serum insulin concentrations during the intravenous glucose tolerance test were measured in duplicate blood samples drawn before and four, six, eight, and 60 minutes after the start of the injection. The insulin index was defined as the ratio of the peak serum insulin concentration (mean of values at four, six, and eight minutes after injection) to the fasting serum insulin concentration.¹² Insulin was measured with a commercially available kit (Phadebas Insulin Test, Pharmacia, Uppsala) on both occasions, but different standards were used. The values from the two investigations were therefore not directly comparable. Changes over time in hypertensive and control groups, however, were calculated and compared by using non-transformed data. For the description of changes in the hypertensive group values are presented as a percentage of the mean value in the control group at the follow up survey, which was taken as 100%.

Serum cholesterol and triglyceride concentrations were measured on a type II Technicon autoanalyser¹⁸ both in samples from the follow up survey and in serum samples which had been stored in liquid nitrogen since the initial survey. Thus the analyses were by the same technique in the two surveys. The frozen samples were analysed at the same time as the samples from the follow up survey.

The cholesterol concentration in high density lipoprotein was assayed in the supernatant after precipitation of the very low and low density lipoproteins with heparin manganese chloride.¹⁹

QUESTIONNAIRE

A self administered medical questionnaire²⁰ was used in the initial health survey to obtain familial and personal medical histories, including data on heritable factors, smoking, and physical activity. The same questions were asked in the follow up survey.

STATISTICAL ANALYSIS

An interaction test²¹ was applied for comparisons of changes between groups and between time points within groups. The model included factors for patient, group, time points, and group-time interaction. In one analysis diabetic state was used as an additional factor.

Results

The average length of the observation period was 9.3 (range 7-11) years for both groups (SD 0.73 for hypertensive men, 0.89 for controls). After nearly 10 years of treatment 79 men were still visiting the hypertension clinic. One died shortly before the re-examination date, one could not attend because of illness, and four failed to attend. Thus 73 hypertensive men were re-examined. Of 78 controls re-examined, 13 were taking thiazides or other blood pressure lowering drugs. Those receiving treatment were excluded from the analysis (none had diabetes); the final control group therefore comprised 65 men, none of whom had had diabetes when seen in 1970-3.

Five controls and two hypertensive men were receiv-

TABLE I—Drug treatments being taken by the 73 hypertensive men at follow up survey (1980-3)

	No treatment	Single drug			Combined treatment with β blocker				
		β Blocker	Thiazide	Hydralazine	Thiazide	Spironolactone	Hydralazine + thiazide	Hydralazine + spironolactone	Other drugs/ combinations
No of men	3	13	3	6	18	3	14	4	9

ing lipid lowering agents at re-examination. These men, along with those who had been given dietary advice during the follow up period (16 hypertensive men only), were also excluded from the final analysis when comparisons were made of metabolic changes over time; dietary treatment and hypolipidaemic drugs may affect serum lipid, glucose, and insulin values.

Treatment of hypertension—Propranolol was given as the first drug in previously untreated subjects. The next step, if required, was to add hydralazine, followed by thiazides if blood pressure was still not satisfactorily controlled. Propranolol was later changed to atenolol

TABLE II—Proportions of 73 hypertensive men receiving different drug treatments during observation period

Drug (singly or in combination)	No (%) of men	Years of use
Propranolol	68 (93)	6.3
Metoprolol or atenolol	47 (64)	2.6
Thiazides or loop diuretics	58 (79)	5.6

TABLE III—Incidence of non-insulin-dependent (type II) diabetes during observation period among attenders at follow up survey (1980-3) stratified by diastolic blood pressure recorded at initial health survey (1970-3)

	Diastolic blood pressure at initial survey (mm Hg)			
	<85	85-94	95-104	≥ 105
No of men*	981	631	91	93
No (%) who developed type II diabetes	25 (2.5)	27 (4.3)	12 (13.1)	13 (14.0)

*Table excludes 64 men who attended for follow up examination, of whom 38 had impaired glucose tolerance at follow up examination and 26 had diabetes at first examination 1970-3.

TABLE IV—Metabolic state of hypertensive and control groups at initial health survey (1970-3) and 95% confidence intervals of estimated differences calculated from adjusted means between matched subjects

Group	No of men	Mean	SD	Estimated difference	95% Confidence interval of estimated difference
<i>Matched variables</i>					
Body mass index (kg/m ²)	Hypertensive 73 Control 65	26.92 26.50	3.47 2.92	0.37	-1.15 to 1.89
Serum triglycerides (mmol/l)	Hypertensive 73 Control 65	2.72 2.54	1.47 1.37	0.17	-0.41 to 0.76
Serum cholesterol (mmol/l)	Hypertensive 73 Control 65	6.82 6.58	1.38 1.05	0.24	-0.24 to 0.71
k Value from intravenous glucose tolerance test	Hypertensive 51 Control 46	1.55 1.60	0.63 0.66	-0.10	-0.47 to 0.27
<i>Non-matched variables</i>					
Body weight (kg)	Hypertensive 73 Control 65	82.48 82.40	11.19 9.63	0.01	-5.79 to 5.31
Abdominal skinfold (mm)	Hypertensive 41 Control 41	26.00 23.70	9.10 11.30	0.64	-8.04 to 9.32
Fasting blood glucose (mmol/l)	Hypertensive 72 Control 65	5.23 5.14	0.79 0.72	0.05	-0.51 to 0.61
Serum insulin (mU/l):					
Fasting	Hypertensive 54 Control 46	18.0 15.7	8.6 11.9	3.0	0.2 to 5.7
Peak value*	Hypertensive 47 Control 44	87.5 71.0	58.6 50.1	22.8	1.3 to 44.3
At 60 minutes in intravenous glucose tolerance test	Hypertensive 54 Control 46	40.5 32.9	21.1 21.5	9.3	-0.0 to 18.6
Insulin index†	Hypertensive 47 Control 44	5.6 5.6	3.6 4.0	0.62	-0.15 to 0.14
High density lipoprotein cholesterol (mmol/l)	Hypertensive 56 Control 49	1.10 1.10	0.35 0.28	-0.01	-0.01 to 0.95

*Peak insulin value is mean of four, six, and eight minute insulin values after start of glucose injection.

†Insulin index is ratio of peak insulin value divided by fasting serum insulin concentration.

or metoprolol in two thirds of patients. Daily doses were in the following ranges: propranolol up to 1280 mg in the first years, then 80-320 mg; hydralazine 50-200 mg; hydrochlorothiazide 12.5-50 mg; atenolol and metoprolol 50-200 mg. Tables I and II give the numbers of patients taking single and combined doses.

Development of diabetes and impaired glucose tolerance—Twelve hypertensive men developed diabetes during the follow up period compared with two of the controls ($p < 0.05$). Two men in each group developed impaired glucose tolerance. Of all 2322 men who took part in the initial health survey, 1860 were re-examined in 1980-3. Of these, 353 men (19%) were receiving treatment with antihypertensive drugs (191 (54%) thiazides, 154 (44%) non-selective β blockers, 125 (35%) selective β blockers). Seventy seven of the 1860 men had developed non-insulin-dependent diabetes mellitus by the time of re-examination. The proportion who developed diabetes among the members of the cohort who were identified as hypertensive in 1970-3 (18/141; 12.7%) was significantly higher than the proportion among the non-hypertensive population (59/1655; 3.6%) ($\chi^2 = 24.6$; $p < 0.001$). None of the 20 hypertensive men who died before re-examination had diabetes recorded in their death certificates.

Heredity—Eighteen per cent of both study groups gave a history of diabetes among first degree relatives (13/73 hypertensive men, 12/65 controls). Four of the 12 hypertensive men who developed diabetes had such a family history.

Time of detection of diabetes—Of the 17 men who were already receiving antihypertensive treatment at the time of the first examination, three developed diabetes. Of the 56 with newly detected hypertension, nine developed diabetes. These proportions were not significantly different on χ^2 testing. There was no evidence that detection and treatment of hypertension earlier than 50 years of age increased the risk of diabetes compared with detection and treatment at age 50.

Development of diabetes in different strata of blood pressure—In the whole cohort of 1860 men who attended follow up there was a positive relation between diastolic blood pressure at first examination and the subsequent development of diabetes (table III). The incidence of diabetes was seven times higher among men whose diastolic blood pressure had been ≥ 105 mm Hg than among those in whom it had been < 85 mm Hg.

Anthropometric and metabolic characteristics—The matching procedure in the case-control study ensured that the mean values in the two groups were similar with respect to body mass index, k value, and serum triglyceride and cholesterol concentrations (table IV). Of the non-matched variables, abdominal skinfold thickness and fasting blood glucose, fasting serum insulin, and high density lipoprotein cholesterol concentrations also did not differ between the groups. The following variables were significantly different in the hypertensive men: blood pressure was higher (systolic 177 v 133 mm Hg, diastolic 111 v 82 mm Hg; both $p < 0.0001$); serum potassium concentration was lower (3.9 v 4.0 mmol/l; $p = 0.013$); peak serum insulin concentration was higher (87.5 v 71.0 mU/l; $p = 0.04$); serum insulin concentration at 60 minutes in the

intravenous glucose tolerance test was higher (40.5 v 32.9 mU/l; $p=0.052$).

Changes in blood pressure, body weight, and metabolic variables over time—At follow up after 7-11 years blood pressure in the hypertensive group had decreased by 20/15 mm Hg (table V), whereas in the control group it had increased by 14/8 mm Hg. Body weight had increased by 2.0 kg in the hypertensive group and 1.3 kg in the controls. The k value remained unaltered in the control group but had decreased in the hypertensive group from 1.71 to 1.28 (-34% ; $p=0.015$). This change, however, was not significantly different from the change in the controls (table V). These comparisons were made after excluding all men who had developed diabetes or who were receiving treatment

TABLE V—Blood pressure and metabolic variables at initial (first) health survey (1970-3) and at follow up (second) survey 7-11 years later, with 95% confidence intervals of estimated differences within groups over time and between groups over time

					95% Confidence interval of:		
					Estimated difference within groups over time	Estimated difference between groups over time	
	No of men*	Mean	SD	Estimated difference			
Systolic blood pressure (mm Hg):							
Hypertensive group	1st Survey	43	175.4	17.1	-20.3	-26.1 to -14.6	-42.1 to -26.8
	2nd Survey	43	155.0	20.8			
Control group	1st Survey	56	133.1	13.2	14.1	9.1 to 19.2	
	2nd Survey	56	147.2	20.5			
Diastolic blood pressure (mm Hg):							
Hypertensive group	1st Survey	43	110.9	8.5	-14.8	-17.5 to -12.0	-25.9 to -18.6
	2nd Survey	43	96.2	7.9			
Control group	1st Survey	59	81.8	8.9	7.5	5.1 to 9.9	
	2nd Survey	59	89.3	9.2			
Body weight (kg):							
Hypertensive group	1st Survey	43	80.23	11.21	2.04	0.52 to 3.55	-0.72 to 3.30
	2nd Survey	43	82.27	11.62			
Control group	1st Survey	59	82.07	10.10	1.29	-0.58 to 2.07	
	2nd Survey	59	82.81	11.38			
Abdominal skinfold (mm):							
Hypertensive group	1st Survey	22	23.69	8.48	7.56	3.48 to 11.66	-4.91 to 5.43
	2nd Survey	43	31.63	8.52			
Control group	1st Survey	37	22.25	10.72	7.30	4.15 to 10.47	
	2nd Survey	56	29.79	10.63			
Fasting blood glucose (mmol/l):							
Hypertensive group	1st Survey	43	5.04	0.62	0.14	-0.02 to 0.31	-0.04 to 0.40
	2nd Survey	42	5.16	0.46			
Control group	1st Survey	56	5.06	0.56	-0.03	-0.18 to 0.10	
	2nd Survey	56	5.02	0.49			
k Value from intravenous glucose tolerance test:							
Hypertensive group	1st Survey	29	1.71	0.66	-0.35	-6.63 to -0.07	-0.63 to 0.11
	2nd Survey	42	1.28	0.52			
Control group	1st Survey	38	1.63	0.66	0.09	-0.34 to 0.15	
	2nd Survey	54	1.64	0.86			
Serum triglycerides (mmol/l):							
Hypertensive group	1st Survey	43	2.29	0.85	0.32	-0.02 to 0.67	0.29 to 1.17
	2nd Survey	41	2.61	1.41			
Control group	1st Survey	56	2.45	1.39	-0.32	-0.72 to -0.10	
	2nd Survey	50	2.04	1.11			
Serum cholesterol (mmol/l):							
Hypertensive group	1st Survey	43	6.76	1.50	-0.32	-0.65 to -0.00	-0.43 to 0.44
	2nd Survey	41	6.42	1.11			
Control group	1st Survey	56	6.62	1.07	-0.32	-0.62 to -0.04	
	2nd Survey	50	6.18	0.98			
High density lipoprotein cholesterol (mmol/l):							
Hypertensive group	1st Survey	34	1.11	0.40	-0.12	-0.24 to 0.00	-0.26 to 0.07
	2nd Survey	40	1.03	0.23			
Control group	1st Survey	43	1.11	0.27	-0.03	-0.14 to 0.08	
	2nd Survey	54	1.08	0.34			

*Table excludes hypertensive men and controls with diabetes or who had received dietary advice or were taking lipid lowering drugs at follow up.

TABLE VI—Relative percentage values of fasting and peak serum insulin concentrations at initial (first) and follow up (second) health surveys in hypertensive men who developed diabetes mellitus or impaired glucose tolerance during observation period and those who did not. Values in controls who did not develop these disorders taken as 100%

		Hypertensive men who developed diabetes or impaired glucose tolerance (n=14)	Hypertensive men who did not develop diabetes or impaired glucose tolerance (n=59)	Controls who did not develop diabetes or impaired glucose tolerance (n=61)*
Relative value of fasting serum insulin (%)†	1st Survey	178	103	100
	2nd Survey	205	146	100
Relative value of peak serum insulin (%)‡	1st Survey	113	134	100
	2nd Survey	62	134	100

*Values in controls assumed to be unchanged over time. Adjustment to 100% done after interaction test.

†Values corrected from second survey.

‡Insulin peak in follow up survey multiplied by 2.153 and transformed into percentage scale where 70.4 mU/l=100%.

with lipid lowering drugs or diet in 1980-3. Serum triglyceride concentration had declined in the control group (2.45 to 2.04 mmol/l) and increased in the hypertensive group (2.29 to 2.61 mmol/l). These changes were significantly different between the groups (table V). Changes in serum cholesterol and high density lipoprotein cholesterol concentrations over time showed no difference between the groups. These findings were consistent whether or not men receiving lipid lowering agents or diet were excluded.

Comparison of men who developed diabetes with those who did not—Review of values obtained at the initial examination showed that the hypertensive men who later developed diabetes (12) or impaired glucose tolerance (two) could be distinguished from the remaining hypertensive men in six main ways: (a) their fasting serum insulin concentration was higher (26.1 v 15.2 mU/l ($p<0.0001$) or 178% v 103% of the control value ($p<0.0001$)) (table VI); (b) their peak serum insulin concentration was lower (78.9 v 94.3 mU/l ($p=0.067$) or 113% v 134% of the control value) (table VI); (c) their insulin index was lower (3.4 v 6.6; 95% confidence interval of difference 1.4 to 5.4); (d) their serum triglyceride concentration was higher (3.43 v 2.56 mmol/l; 95% confidence interval of difference -1.51 to -0.27); (e) their body mass index was higher (28.88 v 26.41; 95% confidence interval of difference -3.10 to -1.58); and (f) their k value was lower (1.29 v 1.68; 95% confidence interval of difference -0.02 to 0.68) (table VII). The four men in the control group who developed diabetes or impaired glucose tolerance also had higher fasting serum insulin concentrations than the remainder of the control group at the initial examination (21.5 v 14.7 mU/l). The small number precluded statistical analysis. There was no difference in fasting blood glucose and serum cholesterol concentrations between those who developed diabetes and those who did not.

Relative changes in serum insulin concentrations during treatment for hypertension—To evaluate the influence of long term antihypertensive treatment on metabolic variables with no interference from diabetes or impaired glucose tolerance we compared the changes over time between non-diabetic men in the hypertensive and control groups. Excluding men who had received hypolipidaemic drugs or dietary advice did not alter the results and they were therefore included in the analysis (table VII). The fasting serum insulin concentration increased in non-diabetic hypertensives compared with non-diabetic controls (table VI), but not significantly. There was no change with time in peak serum insulin concentration in non-diabetic hypertensives relative to controls, though the value in diabetic hypertensives showed a substantial fall ($p<0.0001$) (table VI). The insulin index (table VII) decreased with time in both non-diabetic and diabetic hypertensives compared with non-diabetic controls.

Discussion

The incidence of diabetes mellitus among people with untreated hypertension is not known. In this study, however, the hypertensive men who later developed diabetes differed from those who did not with respect to metabolic variables and showed signs of disturbed glucose metabolism at around the age of 50, many years before the onset of diabetes. Thus they had a higher fasting serum insulin concentration and lower peak serum insulin concentration ($p=0.064$), giving a lower insulin index at the initial examination. They also had a higher body mass index and serum triglyceride concentration and a lower ($p=0.065$), but still normal, k value compared with those hypertensive men who did not develop diabetes. Several of these signs—for example, a high fasting serum insulin

TABLE VII—Laboratory findings in initial (first) and follow up (second) health surveys. Table includes men receiving lipid lowering agents but excludes those who already had diabetes at initial examination (1970-3)

		(A) Hypertensive men who developed diabetes or impaired glucose tolerance (n=14)		95% Confidence interval of difference at first investigation between (A) and (B)	(B) Hypertensive men who did not develop diabetes or impaired glucose tolerance (n=56)		95% Confidence interval of difference over time between (B) and (C)	(C) Controls who did not develop diabetes or impaired glucose tolerance (n=61)	
		Mean	SD		Mean	SD		Mean	SD
Fasting blood glucose (mmol/l)	1st Survey	5.36	0.56	-0.72 to 0.29	5.07	0.66	-0.65 to 0.35	5.06	0.54
	2nd Survey	8.37	3.25		5.15	0.48		5.00	0.49
k Value from intravenous glucose tolerance test	1st Survey	1.29	0.40	-0.02 to 0.68	1.68	0.64	-0.11 to 0.52	1.64	0.66
	2nd Survey	0.71	0.17		1.35	0.56		1.64	0.86
Body mass index (kg/m ²)	1st Survey	28.88	2.80	-3.10 to -1.58	26.41	3.37	-1.11 to 0.21	26.42	2.97
	2nd Survey	28.74	2.56		27.13	3.51		26.69	3.35
Serum triglycerides (mmol/l)	1st Survey	3.43	2.39	-1.51 to -0.27	2.56	1.15	-1.16 to -0.03	2.48	1.34
	2nd Survey	3.73	2.02		2.74	1.42		2.03	1.08
Serum cholesterol (mmol/l)	1st Survey	6.48	1.37	-0.06 to 0.79	6.84	1.39	-0.30 to 0.47	6.56	1.07
	2nd Survey	6.38	1.30		6.46	1.10		6.17	0.95
Insulin index	1st Survey	3.40	2.20	1.40 to 5.40	6.60	3.60	0.30 to 3.80	5.80	4.00
	2nd Survey	1.90	1.80		5.00	2.90		5.90	3.90

concentration and an increased serum triglyceride concentration—indicate increased insensitivity to insulin. The sensitivity to insulin as measured by the hyperinsulinaemic euglycaemic clamp technique is reduced in the hypertensive state even after correction for a higher body mass index. Reduced sensitivity to insulin may therefore be a primary state in people with hypertension. Furthermore, a low insulin index has been regarded as an early prognostic sign of the later development of non-insulin-dependent (type II) diabetes mellitus.²²

In our subgroup of treated hypertensive men who did not develop diabetes the insulin index and serum triglyceride concentration changed in a different way from that in the control group despite the two groups having been similar at the start. That the changes were different in the hypertensive men supports but does not prove the hypothesis that the changes were the effects of long term treatment. It may be a feature of hypertensive men that insulin sensitivity worsens with time. This worsening, however, is probably not related to the hypertensive state itself, as the blood pressure decreased in the hypertensive group and increased in the controls, and these changes should have resulted in the opposite alterations in insulin values to those that were actually found. These data therefore offer some support to the view that today's first line antihypertensive drugs may cause a decrease in insulin sensitivity which does not disappear with time and may elicit the development of diabetes mellitus, particularly in men already predisposed to the disease.

There are conflicting data on whether the effects of drugs on lipoprotein metabolism disappear with time. In one study, for example, the changes in serum lipid values detected after six months of treatment with chlorthalidone had vanished after two years of treatment.²³ By contrast, in the multiple risk factor intervention trial dietary treatment of hyperlipidaemia reversed the changes induced by antihypertensive drugs but the plasma lipid values did not reach as low as in a comparison group that was also given dietary treatment but no antihypertensive drugs. Thus antihypertensive pharmacotherapy counteracted dietary treatment so that the hypertensive group still had higher serum triglyceride and lower high density lipoprotein cholesterol concentrations than the comparison group six years after the start of treatment.¹¹ In our study even after treatment for almost 10 years the change in serum triglyceride values over time differed significantly between the hypertensive and control groups. Serum triglyceride concentrations increased among non-diabetic hypertensive men but decreased among non-diabetic controls ($p<0.02$).

The risk factor pattern for coronary heart disease in hypertensive men is improved by antihypertensive

treatment in so far as the blood pressure is reduced. But the increased risk of coronary heart disease associated with raised blood pressure may not depend on the blood pressure alone. High blood pressure is only one aspect of a metabolic syndrome which is also characterised by a raised serum insulin concentration and increased serum triglyceride values, and all these aspects may be related to decreased insulin sensitivity. Possibly the other characteristics of the syndrome may have been underestimated as risk factors for coronary heart disease. Increased serum insulin and triglyceride concentrations have been found to be risk factors in prospective epidemiological studies.²⁴⁻²⁸ If antihypertensive treatment as used in this study is associated with a deterioration of the other features of the metabolic syndrome such changes may partly explain the failure of many studies on treatment of hypertension to reduce the incidence of coronary heart disease.

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Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients

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Abstract

Objective—To compare the effects of metoprolol and atenolol on carbohydrate and lipid metabolism and on insulin response to an intravenous glucose load.

Design—Randomised, double blind, double dummy, controlled crossover trial.

Setting—University Hospital, Uppsala, Sweden.

Patients—60 Patients with primary hypertension (diastolic blood pressure when resting supine 95-119 mm Hg on at least two occasions during four to six weeks of treatment with placebo) randomised to receive either metoprolol (n=30) or atenolol (n=30) during the first treatment period.

Interventions—Placebo was given for a run in period of four to six weeks. Metoprolol 100 mg twice daily or atenolol 25 mg twice daily was then given for 16 weeks. The two drugs were then exchanged and treatment continued for a further 16 weeks.

End point—Evaluation of effects of treatment with metoprolol and atenolol on glucose, insulin, and lipid metabolism and glucose disposal mediated by insulin.

Measurements and main results—Reduction of blood pressure was similar and satisfactory during treatment with both drugs. Glucose uptake mediated by insulin was measured during a euglycaemic hyperinsulinaemic clamp to evaluate patients' sensitivity to insulin. Glucose uptake decreased from 5.6 to 4.5 mg/kg/min when patients were taking metoprolol and from 5.6 to 4.9 mg/kg/min when they were taking atenolol. Both drugs caused a small increase in fasting plasma insulin and blood glucose concentrations and glycated haemoglobin concentration. Despite decreased sensitivity to insulin the increase in insulin concentration in response to an intravenous glucose tolerance test was small, suggesting inhibition of release of insulin. Very low density lipoprotein and low density lipoprotein triglyceride concentrations were increased with both drugs and high density lipoprotein cholesterol concentration was decreased. Low density lipoprotein cholesterol concentration was not affected.

Conclusions—Long term use of metoprolol and atenolol causes metabolic abnormalities that may be related to the increased incidence of diabetes in patients with hypertension who are treated pharmacologically. These results may help to explain why the two drugs have failed consistently to reduce

the incidence of coronary heart disease in several large scale studies.

Introduction

During the past 20 years there has been much emphasis on detecting and treating hypertension, which is an important risk factor for cardiovascular disease,¹ and several large scale trials have shown that a reduction in blood pressure is associated with a decrease in cardiovascular morbidity and mortality.²⁻⁵ Some of the drugs used to treat hypertension, however, have adverse effects, including disturbances of serum lipid concentrations and glucose metabolism.^{5,7} Treatment with thiazide diuretics and β blockers has been associated with an increased incidence of impaired glucose tolerance⁶ and diabetes.^{5,7} Few attempts have been made, however, to evaluate specific influences of pharmacological treatment of hypertension on glucose metabolism—for example, to determine whether it decreases secretion of insulin or sensitivity to insulin, or both. Sensitivity to insulin may be important as studies have shown that hypertension is accompanied by resistance to insulin.⁸⁻¹⁰

We evaluated the effect of long term treatment with two widely used β_1 adrenergic blockers, metoprolol and atenolol, on glucose disposal mediated by insulin and examined their effects on glucose, insulin, and lipid metabolism.

Patients and methods

CRITERIA FOR INCLUSION

Patients were recruited from a health screening survey in Uppsala, Sweden. All had primary hypertension, defined as a stable diastolic blood pressure when resting supine of 95-119 mm Hg on at least two occasions during four to six weeks of treatment with placebo. Any current antihypertensive treatment was stopped and a placebo was given single blind for four to six weeks. Patients with newly detected hypertension were followed up for three to four months to make sure that their raised blood pressure was stable before they entered the single blind placebo period.

CRITERIA FOR EXCLUSION

Criteria for exclusion were: clinical or laboratory evidence of hepatic or renal disease, obstructive pulmonary disease, Raynaud's disease, or thyroid dys-

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