

Insulin, hypertension and antihypertensive drugs in elderly patients: the Rotterdam Study

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Objective To investigate the association between insulin, hypertension and antihypertensive drug use in elderly patients.

Design and methods Blood pressure, use of antihypertensive drugs and glucose metabolism were examined in 5453 men and women (mean age 68.8 years). This was part of the baseline examination of the Rotterdam Study, a population-based study of chronic diseases in elderly patients. Serum insulin was measured 2 h after an oral glucose load.

Results Patients with hypertension had a significantly higher mean post-load insulin level than those without: 71.3 mU/l versus 59.3 mU/l ($P < 0.001$, adjusted for age). Systolic blood pressure increased by 0.25 mmHg per 10 mU/l insulin (95% confidence interval 0.15–0.35, adjusted for age, sex and antihypertensive drugs), whereas the increase in diastolic blood was 0.07 mmHg per 10 mU/l (0.01–0.13). Whereas insulin resistance was higher in patients with hypertension, the increase in insulin resistance with age was much more apparent in normotensive patients, resulting in similar insulin levels at high ages. Those using antihypertensive drugs, however, had higher insulin levels at all ages.

Introduction

Raised insulin resistance and resulting hyperinsulinemia in patients with hypertension has repeatedly been demonstrated [1,2]. Most of these studies, however, have been performed in middle-aged patients. Non-insulin-dependent diabetes mellitus (NIDDM) is common in elderly people, as is hyperinsulinemia [3], which precedes the onset of NIDDM [4]. Moreover, the prevalence of hypertension and of the use of antihypertensive drugs increases steeply with increasing age [5]. Because many antihypertensive drugs influence glucose metabolism [6], this may further worsen the metabolic condition in elderly people. On the other hand, one may wonder whether the association between insulin and blood pressure is still present in those patients who survive until older ages, and whether antihypertensive drugs still have an adverse effect on glucose metabolism in elderly patients.

To study the influence of antihypertensive drugs and blood pressure level on glucose metabolism in elderly

Conclusion The results of this study show that hyperinsulinemia is associated with raised blood pressure in elderly people, and suggest that the age-associated increase in insulin resistance is diminished in patients with raised blood pressure. The use of antihypertensive drugs, however, appears to be accompanied by an independent additional increase in insulin resistance at all ages.

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patients, we examined these variables as part of the population-based Rotterdam Study. This paper describes the associations of insulin resistance with hypertension and the use of antihypertensive drugs.

Material and methods

Study population

The Rotterdam Study is a population-based cohort study of determinants of chronic disabling diseases in elderly people. All inhabitants of a suburb of Rotterdam aged 55 years and over were invited to participate. An outline of the study and its objectives has been published previously [7]. The baseline examination of the Rotterdam Study was conducted from 1990 to 1993. The participants were interviewed in their homes by trained research assistants, using a computerized questionnaire, which included an assessment of current medication use. Subsequently the participants came to the research center for several measurements, including blood pressure. In addition, a non-fasting oral glucose tolerance test was performed,

which was introduced a few months after the start of the study. Informed consent was obtained from all patients and the study was approved by the medical ethics committee of the Erasmus University Medical School. Overall, 7983 participants were examined in the Rotterdam Study (response rate 78%). The present analyses are restricted to the 5453 patients not receiving drug treatment for diabetes mellitus, in whom serum insulin levels and blood pressure were measured.

Measurements

During the home interview participants were asked to show all medications they were taking at that time. Information about generic and trade names was entered into the database using the ATC (Anatomical Therapeutic Chemical) classification index codes [8]. The data were verified by a physician at the research center, who also recorded the indication for the used medication. For the present analyses antihypertensive drugs were classified into diuretics (ATC code C03), β -blockers (C07), angiotensin converting enzyme (ACE) inhibitors (C02EA) and calcium antagonists (C02DE). Other antihypertensive drugs (e.g. α -blockers) were seldom prescribed.

The participants came to the research center throughout the day irrespective of the time of their last meal. Therefore, most participants were non-fasting. Blood was drawn by venepuncture and patients not taking antidiabetes medication (tablets or insulin) received a drink containing 75 g of glucose. Two hours later a second blood sample was obtained. Glucose levels were measured in both samples by the glucose hexokinase method, whereas insulin was measured by radioimmunoassay (Medgenix Diagnostics, Brussels, Belgium) in the post-load sample only. Diabetes mellitus was defined as use of antidiabetes medication or a random or post-load serum glucose level of 11.1 mmol/l or over. Insulin resistance was assessed by post-load insulin level and the ratio of post-load insulin to glucose. Sitting blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. The mean of two measurements obtained on one occasion, separated by an assessment of the pulse rate, was used in the analyses. Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of medication for hypertension. Body mass index was calculated as weight (with indoor clothing) divided by the square of height (kg/m^2).

Data analysis

Analysis of covariance was used to estimate the age-adjusted baseline characteristics of patients with and without hypertension, as well as adjusted mean values by groups of hypertension and antihypertensive drugs. Multiple linear regression analysis was used to assess the associations between age, blood pressure and insulin, as well as to adjust blood pressure level for use of

antihypertensive drugs. The results are presented as regression coefficients with 95% confidence interval. The difference in the use of antihypertensive drugs with increasing age was estimated by logistic regression analysis with odds ratios as an approximation of relative risk. Insulin resistance was compared between patients with and without hypertension in strata of age by *t*-tests. The association between age and insulin was further examined by stratified linear regression analysis.

Results

Hypertension was present in 1554 of the participants (28.5%), 560 men (25.5%) and 994 women (30.5%). In Table 1 the baseline characteristics of the study population are given by the presence of hypertension. All measures of glucose metabolism were significantly higher in patients with hypertension than in those without, which remained after adjustment for age, gender and body mass index ($P < 0.0001$).

Post-load serum insulin increased by 0.87 mU/l for each year of age (95% confidence interval 0.71–1.03 mU/l, adjusted for sex). In men and women the increase was 0.57 mU/l (95% confidence interval 0.32–0.83 mU/l) and 1.02 mU/l (95% confidence interval 0.82–1.22 mU/l) respectively. The associations were essentially the same if the ratio of insulin to glucose was used as a measure of insulin resistance. The proportion of patients using antihypertensive drugs increased with age (by 23% per 10 years of age, 95% confidence interval 13–34%). In men the corresponding relative risk was 1.14 (95% confidence

Table 1 Baseline characteristics of the study population by presence or absence of hypertension

	Hypertension*	
	Present	Absent
Number	1554	3899
Women	64%	58.0%
Age (years)	71.0 (0.22)	68.0 (0.14)
Body mass index (kg/m^2)	27.2 (0.12)	26.0 (0.06)
Random serum glucose (mmol/l)	6.9 (0.06)	6.6 (0.03)
Post-load serum insulin (mU/l)	71.3 (1.45)	59.3 (0.81)
Ratio of post-load insulin to glucose (mU/mmol)	9.7 (0.17)	8.7 (0.10)
Diabetes mellitus [†]	11.0%	5.5%
Systolic blood pressure (mmHg) [‡]	160.0 (0.55)	130.4 (0.26)
Diastolic blood pressure (mmHg) [‡]	81.4 (0.30)	70.7 (0.16)
Use of antihypertensive medication		
For hypertension	58.9%	
For any indication	63.5%	18.0%
Diuretics	29.7%	9.7%
β -Blockers	29.9%	8.0%
ACE inhibitors	13.3%	2.7%
Calcium antagonists	9.2%	4.8%

*Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg or use of antihypertensive medication. Values are means with standard error in parenthesis. [†]Random or post-load glucose level ≥ 11.1 mmol/l, only in subjects who were not receiving antidiabetes medication. [‡]Subjects taking antihypertensive medication included.

interval 0.98–1.34), whereas in women it was found to be 1.26 (95% confidence interval 1.14–1.40).

Post-load insulin levels were associated with systolic blood pressure level (coefficient of linear regression 0.25 mmHg per 10 mU/l; 95% confidence interval 0.15–0.35 mU/l, adjusted for age, sex and antihypertensive drug use). For diastolic blood pressure the change was 0.07 mmHg per 10 mU/l (95% confidence interval 0.01–0.13 mU/l). In men coefficients for systolic and diastolic blood pressure were 0.16 mmHg per 10 mU/l (95% confidence interval –0.04–0.36 mmHg, adjusted for age and antihypertensive drug use) and 0.03 mmHg per 10 mU/l (95% confidence interval –0.07–0.13 mmHg) respectively. In women the corresponding regression coefficients were 0.29 mmHg per 10 mU/l (95% confidence interval 0.15–0.43 mmHg) and 0.09 mmHg per 10 mU/l (95% confidence interval 0.01–0.17 mmHg). If patients with diabetes mellitus were excluded from the analyses, the results remained essentially the same.

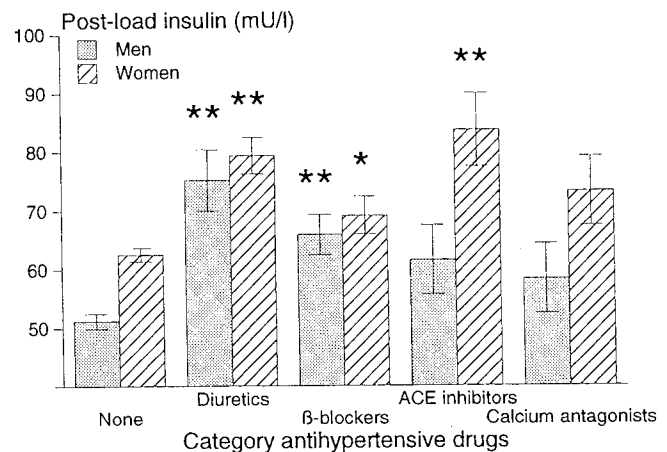
Patients with hypertension taking antihypertensive drugs had higher post-load insulin levels than those with hypertension but not currently using antihypertensive drugs (74.9 versus 67.2 mU/l, $P < 0.01$). Mean insulin levels in patients without hypertension were considerably lower than in both hypertensive subgroups (59.3 mU/l, for both comparisons $P < 0.0001$). The same pattern was found in men and women separately, or after adjustment for age and systolic blood pressure, or when the ratio of insulin to glucose was used as measure of insulin resistance. Insulin levels in patients taking antihypertensive drugs for angina pectoris (20% of the users) were the same as in patients taking these drugs for hypertension (60%). Patients being treated with antihypertensive drugs for heart failure (15%) had even higher insulin levels than patients taking these drugs for hypertension: 91.0 mU/l ($P < 0.01$, adjusted for age, sex and systolic blood pressure).

Table 2 gives some characteristics of the users of four major groups of antihypertensive drugs. As expected, in spite of the medication, mean blood pressure was higher in users than in non-users. Users of antihypertensive drugs

also had higher mean insulin levels. In Figure 1 the insulin levels, adjusted for age and systolic blood pressure, are given for patients taking four groups of antihypertensive drugs. In both men and women insulin levels were significantly higher in those who used diuretics and β -blockers than in patients who did not use antihypertensive drugs. This was also found for thiazides and loop diuretics separately (data not shown). Women using ACE inhibitors also had higher insulin levels. The same results were found after adjustment of insulin levels for diastolic blood pressure.

In Figure 2 mean insulin levels are given by 5 year age categories for patients with and without hypertension. The number of patients in each category ranged from 66 to 680. The difference in insulin levels between women with and without hypertension decreased with age, and disappeared in very old patients (75 years and older). When examined more closely, it appeared that the increase in insulin level with age was much more apparent in those without

Fig. 1.



Mean post-load insulin levels, adjusted for systolic blood pressure, by group of antihypertensive drug use. Values are means with standard error. Patients using combinations of antihypertensive drugs were excluded from the analysis. ** $P < 0.01$ compared with patients of the same sex not taking antihypertensive drugs, adjusted for age and systolic blood pressure.

Table 2 Selected clinical characteristics, by category of antihypertensive drug use.

	None	Diuretics	β -Blockers	ACE inhibitors	Calcium antagonists
Number	3701	377	458	138	144
Women	58.3%	76.7% [†]	58.1%	50.1%	54.2%
Age (years)	67.7 (0.1)	74.8 [†] (0.5)	68.6* (0.4)	69.3 [†] (8.2)	72.3 [†] (0.7)
Systolic blood pressure (mmHg)	136.9 (0.4)	142.5 (1.1)	143.5 [†] (1.1)	151.7 [†] (1.9)	142.3 (1.9)
Diastolic blood pressure (mmHg)	73.5 (0.2)	72.8 (0.6)	75.9 [†] (0.5)	79.0 [†] (1.0)	73.6 (1.0)
Hypertension [†]	16.5%	51.5% [†]	58.5*	73.2 [†]	40.3 [†]
Post-load insulin (mU/l)	57.1 (0.8)	83.1 [†] (3.2)	68.8 [†] (3.0)	75.9 [†] (6.7)	69.4 (5.1)

Values are means with standard error in parentheses. Subjects using combinations of antihypertensive drugs were excluded from the analysis (n=635). * $P < 0.05$, [†] $P < 0.01$, compared with subjects not taking antihypertensive drugs, adjusted for age and sex. [‡]Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg or use of hypertensive medication for hypertension.

Fig. 2.

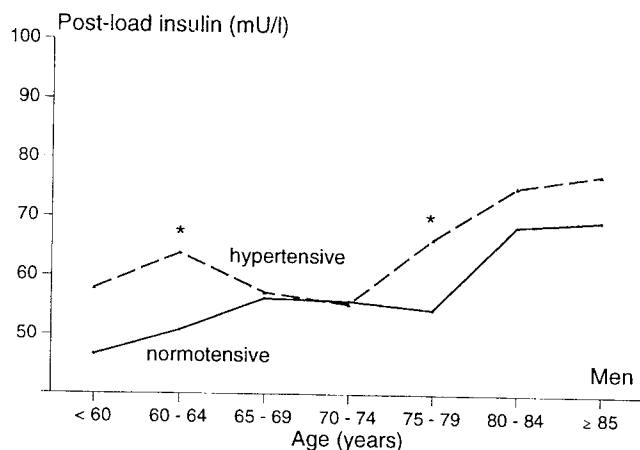
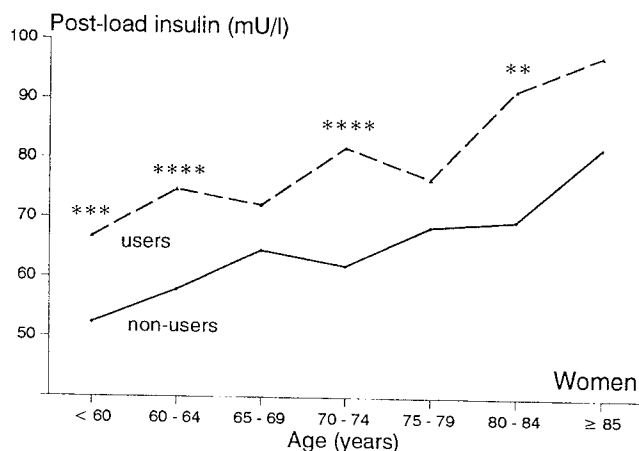
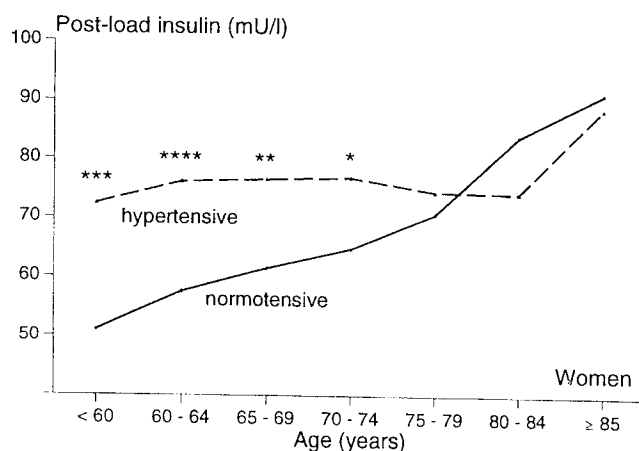
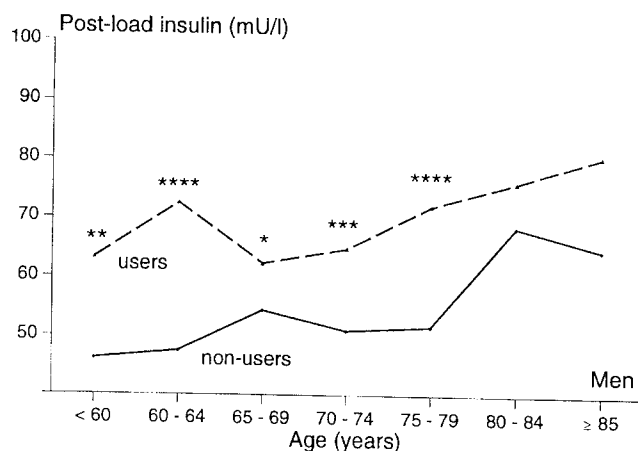


Fig. 3.



Mean post-load insulin levels by 5 year age categories for patients with and without hypertension. Difference between patients with and without hypertension: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$, **** $P < 0.001$.

Mean post-load insulin levels, adjusted for systolic blood pressure, by 5 year age categories, for patients who did and did not use antihypertensive drugs. Difference between patients who did and did not use antihypertensive drugs: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$, **** $P < 0.001$.

hypertension: in normotensive men insulin increased by 0.61 mU/l per year (95% confidence interval 0.32–0.90 mU/l), whereas an increase of 0.40 mU/l per year (95% confidence interval –0.15–0.95 mU/l) was found in hypertensive men. This difference was more pronounced in women: 1.16 mU/l per year (95% confidence interval 0.93–1.40 mU/l) in normotensive women compared with 0.26 mU/l per year (95% confidence interval –0.15–0.67 mU/l) in women with hypertension. Figure 3 gives the insulin levels, adjusted for systolic blood pressure, for patients who did and did not use antihypertensive drugs. The figure shows that both male and female antihypertensive drug users had higher insulin levels at all ages. An increase in insulin resistance with age occurred in both users and non-users.

Discussion

In this population-based study of 5453 elderly men and women who did not use antidiabetes medication, insulin resistance was assessed using an oral glucose tolerance test. Insulin resistance (estimated by post-load insulin levels and the ratio of post-load insulin to glucose) and the use of antihypertensive drugs increased with age. Higher insulin levels were associated with increased systolic and diastolic blood pressure and the presence of hypertension. However, the age-associated increase in insulin resistance was much more apparent in patients without than in those with hypertension. This results in similar insulin levels in very old hypertensive and normotensive study participants. Patients using antihypertensive drugs have higher insulin levels at all ages, even after adjustment for blood pressure.

A limitation of the Rotterdam Study is the use of a non-fasting blood sample. To overcome this disadvantage, insulin was measured 2 h after an oral glucose load. We reported previously that these insulin levels are similar to the fasting post-load levels [9]. Insulin resistance was assessed by post-load insulin level and the ratio of post-load insulin to glucose. In patients without diabetes mellitus these are good measures of insulin resistance [10]. The indication for the antihypertensive medication used was obtained from the participants, which may have introduced some misclassification. The presented analyses are based on cross-sectional data, which means that no direct causal relationship can be established.

The increase in insulin resistance with age has been described in other population-based studies and is thought to be a general phenomenon of aging [11]. The association between serum insulin and blood pressure is well known [12,13], and has been discussed in several recent reviews [2,6,14]. Most studies, however, have included only middle-aged patients. In the elderly study population of Rancho Bernardo, a similar association between hypertension and post-load insulin levels was found [15]. However, the association was no longer statistically significant after adjustment for age, sex, obesity, and glucose tolerance. In obese elderly patients, hypertension was associated with a decrease in both insulin sensitivity and maximal responsiveness to insulin [16]. The results of these studies and our study suggest that the association between insulin and blood pressure remains at higher ages.

Findings from several other studies strengthen the hypothesis that insulin resistance is related to blood pressure. The prevalence of hypertension is increased in patients with impaired glucose tolerance and NIDDM [17]. Moreover, blood pressure is reduced by metformin in hypertensive patients without diabetes mellitus [18], and in diabetic hypertensive patients reducing the amount of administered insulin lowers blood pressure [19]. Both of these studies, however, were uncontrolled and included very few patients. Insulin may increase blood pressure by causing changes in the vascular muscle cells, renal retention of sodium and water, activation of the sympathetic nervous system, and modification of cation fluxes across cell membranes [20,21]. The association between insulin and blood pressure, however, forms part of a cluster of cardiovascular risk factors, which finally results in hypertension, diabetes mellitus, obesity, and dyslipidemia [1,22]. The sequence of occurrence of the components of this syndrome is still poorly understood.

The use of several antihypertensive drugs is associated with adverse effects on glucose metabolism [6,23] and the development of NIDDM [24,25]. Figure 3 shows that also at advanced age insulin resistance is increased in patients taking antihypertensive drugs. The pathophysiologic mechanisms to explain the increase in insulin resistance

caused by the different drugs are not well known. Among others, blood flow to skeletal muscles, serum electrolytes, and bradykinin might be involved [6,26]. It has been suggested that drug-induced worsening of glucose metabolism may be an explanation for the lower than expected reduction in morbidity and mortality from coronary heart disease in trials of mild to moderate hypertension [27]. The hypothesis that the diabetogenic effect is restricted to diuretics and β -blockers is not supported by our findings (Fig. 1). However, these results must be interpreted cautiously, because the current study was not designed to study the association between use of antihypertensive drugs and insulin resistance. In particular, confounding by indication may pose a serious problem in this analysis. Those patients with more severe hypertension (e.g. long-lasting, difficult to control) or with an increased risk for diabetes mellitus (e.g. obese patients or those with a positive family history) are more likely to receive the newer classes of antihypertensive drugs. In addition, in the present analyses dose and duration of the antihypertensive medication were not taken into account. It has been shown that low doses of diuretics have the same effect on blood pressure as conventional doses, without influencing insulin sensitivity [28].

Differences in insulin level between those taking antihypertensive drugs for hypertension and other indications are difficult to interpret, because the other indications may have been accompanied by an increased blood pressure. However, it has been reported that heart failure is associated with increased insulin resistance [29,30].

The finding that insulin levels apparently did not further increase with age in those patients with hypertension suggests that insulin resistance has an upper limit, which could be reached by either antihypertensive drug use or aging. This upper limit may reflect the development of non-insulin-dependent diabetes mellitus, which is considered as a state of severe insulin resistance [31]. Alternatively, the upper limit of beta-cell secretion might be reached by either of these two mechanisms. In the present study, it is not possible to disentangle insulin resistance and insulin secretion. However, because patients receiving drug treatment for diabetes mellitus were excluded, it is unlikely that beta-cell failure is common in our study population.

In conclusion, the results of this study show that hyperinsulinemia is associated with raised blood pressure in the elderly, and suggest that the age-associated increase in insulin resistance is diminished in patients with raised blood pressure. In addition, the use of antihypertensive drugs appears to be accompanied by an independent additional increase in insulin resistance at all ages. Follow-up studies are needed to assess further the effects of age and the different classes of antihypertensive drugs on insulin resistance in elderly people.

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