Diabetologia (1995) 38: 839–847

Diabetologia

Hypertension and overweight associated with hyperinsulinaemia and glucose tolerance: a longitudinal study of the Finnish and Dutch cohorts of the Seven Countries Study

E. J. M. Feskens[1], J. Tuomilehto[2], J. H. Stengård[2], J. Pekkanen[3], A. Nissinen[4], D. Kromhout[1]

[1] Department of Chronic Diseases and Environmental Epidemiology, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands
[2] Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland
[3] Department of Environmental Epidemiology, National Public Health Institute, Kuopio, Finland
[4] Department of Community Health and General Practice, University of Kuopio, Kuopio, Finland

Summary To elucidate the role of hypertension as part of the insulin resistance syndrome, the longitudinal relationships of hypertension and overweight with hyperinsulinaemia and glucose tolerance were examined in the Dutch and Finnish cohorts of the Seven Countries Study (Zutphen, and east and west Finland). Three cohorts of men, born between 1900 and 1919, were first examined in 1959/1960. At the 30-year follow-up survey a 2-h glucose tolerance test was carried out on 619 of the surviving men, and fasting insulin was also measured. Blood pressure and body mass index (BMI) were measured several times during the entire 30-year follow-up period. In cross-sectional analyses, men with diabetes and impaired glucose tolerance at the 30-year follow-up examination had a significantly higher systolic blood pressure and a higher prevalence of hypertension than men with normal glucose tolerance, independent of age, cohort and BMI ($p < 0.01$). These differences had already been seen 5, 20 and 30 years earlier. Subjects with hyperinsulinaemia (fasting insulin $\geq$ 9.2 mU/l) had a higher BMI and a higher prevalence of hypertension. This cross-sectional association with hypertension was independent of age, cohort and BMI. BMI levels of men with hyperinsulinaemia had been shown to be higher 5, 20 and 30 years earlier, but blood pressure levels had not. These results indicate that hypertension is independently associated with glucose tolerance and insulin resistance in three Caucasian cohorts. Changes in blood pressure precede abnormal glucose tolerance but not hyperinsulinaemia; therefore, glucose tolerance appears to be a stronger correlate of hypertension than hyperinsulinaemia. [Diabetologia (1995) 38: 839–847]

Key words Non-insulin-dependent diabetes mellitus, hypertension, insulin, longitudinal, overweight.

Macrovascular complications are common in diabetic patients, and it is well established that cardiovascular risk factors tend to cluster in diabetic individuals. Recently, an aetiologic theory for this observation has been provided [1]. According to this view, insulin resistance and hyperinsulinaemia are underlying metabolic risk factors responsible for impaired glucose tolerance as well as dyslipidaemia and hypertension, all leading to increased risk of non-insulin-dependent diabetes mellitus (NIDDM) and coronary heart disease. This cluster of risk factors is frequently referred to as 'syndrome X', or the insulin resistance syndrome [1–5].

The relation between insulin and hypertension seems, however, to be controversial [6]. Fasting serum insulin was associated with hypertension in an Israeli population [7], and insulin resistance was observed among lean hypertensive patients [8–10], but a number of other epidemiologic studies have failed to confirm these observations [11–13]. Most of these studies were cross-sectional in nature, and cause and effect were thus difficult to disentangle.

Longitudinal and prospective studies on this issue are scarce. One prospective study has been reported,

Received: 20 July 1994 and in revised form: 17 January 1995

Corresponding author: Dr. E. J. M. Feskens, Department of Chronic Diseases and Environmental Epidemiology, National Institute of Public Health and Environmental Protection, P. O. Box 1, NL-3720 BA Bilthoven, The Netherlands

Abbreviations: GTT, Glucose tolerance test; BMI, body mass index; NIDDM, non-insulin-dependent diabetes mellitus.

and in this study fasting insulin was not an independent risk factor for hypertension after adjustment for overweight and body fat distribution, although an independent association was observed in a subgroup with normal body weight and normoglycaemia [5]. In the same study population it was observed that hypertension was an independent predictor of the incidence of impaired glucose tolerance, but not of diabetes [14]. The relation with the risk of developing hyperinsulinaemia was not investigated.

The Finnish and Dutch cohorts of the Seven Countries Study have been followed-up since 1959/1960 [15]. A 30-year follow-up survey among the survivors was recently completed. These data provided an opportunity to elucidate the longitudinal relationships of hypertension with glucose tolerance and hyperinsulinaemia. Effect modification by overweight was also investigated.

Subjects and methods

Study populations. The Seven Countries Study was initiated by Ancel Keys as a cardiovascular risk factor survey among 16 cohorts of middle-aged men in seven different countries [15, 16]. The study started in the period 1958–1964. At the baseline examination and at the 5- and 10-year follow-up examinations the participants were examined using a standardized protocol [16]. The survivors of the cohorts in Finland and the Netherlands were re-examined after 25 and 30 years using an extended protocol.

In Finland, the original cohorts in 1959 consisted of all men born in 1900–1919 from two geographically defined areas, Ilomantsi in eastern Finland ($n = 823$) and Pöytyä and Mellilä in western Finland ($n = 888$). In 1984, 321 men aged 65–84 years were re-examined in east Finland, and 395 men in west Finland. In 1989, at the time of the latest follow-up the subjects were 70–89 years old. Altogether 524 men of the original cohort of 1711 men were still alive. Of these, 470 (90 %) were examined.

The Dutch cohort comes from the town of Zutphen, in the eastern part of the country. Of this cohort, 878 men were examined for the first time in 1960, 446 (51 %) were still alive in 1985. 380 (85 %) of them participated in the examination. All 314 participants alive in 1990 were invited for the 30-year follow-up examination and 238 (76 %) of them took part in the re-examination.

Examinations. All the men were examined according to the international protocol used in previous surveys of the Seven Countries Study [15]. Briefly, this examination included a medical history, a physical examination, measurement of weight, height, blood pressure, and a venous blood sample. Information about smoking habits was also collected.

At the 30-year follow-up survey, an oral glucose tolerance test (GTT) was carried out, according to the World Health Organization (WHO) guidelines [17]. Subjects treated with insulin or oral hypoglycaemic agents were considered diabetic and were excluded from the GTT. The first blood sample was obtained in the morning after an overnight fast. The second sample was obtained 2 h after a glucose load of 75 g. Samples were collected in tubes with sodium fluoride. Plasma glucose was determined in Finland using the glucose dehydrogenase method (Glucose Analyzer II, Beckman, Brea, Ca. USA). In the Netherlands, plasma glucose was determined by the hexokinase method in a routine laboratory. Insulin was measured separately in the Finnish and Dutch laboratories in sera collected at fasting. In both laboratories a radioimmune-assay from Pharmacia Diagnostics, Uppsala, Sweden, was used. Serum samples were exchanged for calibration, and the resulting regression equation was used to adjust the Finnish values ($1.85 + 0.70$ old value, $r = 0.991$).

According to the WHO criteria for diabetes [17] men with a 2-h plasma glucose level of 11.1 mmol/l or more were considered as newly-diagnosed diabetic subjects, and those with 2-h plasma glucose levels between 7.8 and 11.1 mmol/l as having impaired glucose tolerance (IGT). Men with 2-h plasma glucose below 7.8 mmol/l were considered to be normoglycaemic (NGT, normal glucose tolerance). Hyperinsulinaemia was defined as the 75th-percentile of fasting insulin level of the lean study population (present BMI ≤ 25 kg/m^2) without diabetes, i.e. a level ≥ 9.2 mU/l.

Physical examinations were performed by trained physicians. Height and weight were measured in light clothing without shoes. BMI was calculated by dividing weight by height squared (kg/m^2). Blood pressure was measured with each man in supine position after 5 min rest from the right arm. At all Finnish surveys and at the baseline, 5- and 10-year follow-up surveys in the Netherlands a standard mercury sphygmomanometer was used. The mean value of two measurements was recorded. At the 25- and 30-year follow-up examinations in the Netherlands a random zero device was used. Diastolic blood pressure was recorded as the fifth Korotkoff phase. Drug treatment for hypertension was recorded at the 25-year and 30-year follow-up. Hypertension was defined as either systolic blood pressure 160 mm Hg or more or diastolic blood pressure 95 mm Hg or more or being on antihypertensive drug treatment regardless of the blood pressure values [18].

During the 30-year follow-up survey, serum total and HDL-cholesterol was determined in fasting samples in Finland, whereas in the Netherlands a non-fasting sample was taken. Triglycerides were measured in fasting serum samples. In both countries the cholesterol determinations were carried out in lipid laboratories standardized according to the WHO criteria Lipid Reference Laboratories in Prague (for the Helsinki laboratory) or Centers for Disease Control, Atlanta, Georgia, USA (for the Dutch laboratory). In both laboratories serum total cholesterol and triglycerides were determined enzymatically [19, 20]. HDL-cholesterol was determined after precipitation of the apo-B containing lipoproteins with dextran magnesium chloride (Finland) or dextran magnesium sulphate (Netherlands) [21].

Standardized questions on the history of hypertension and diabetes mellitus were asked [22]. In Finland the standardized questionnaire of the Seven Countries Study core protocol was used to obtain information on smoking habits [15]. In the Netherlands information on smoking habits was collected using a locally developed questionnaire.

Statistical analyses

Statistical analyses were carried out using the SAS-programmes version 6.07 [23]. The total number of men examined at the 30-year follow-up survey was 708. Due to missing data the number of subjects was reduced to 608 when investigating glucose tolerance and diabetes mellitus. For the analysis of hyperinsulinaemia the treated diabetic patients were excluded, since fasting insulin levels are an indicator of insulin resistance in non-diabetic subjects only. Men treated with diet only were to consid-

Table 1. Prevalence of diabetes mellitus and impaired glucose tolerance among men aged 70–89 years at the 30-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study (1989/1990)

	east Finland		west Finland		Zutphen (NL)	
	n	%	*n*	%	*n*	%
Normal glucose tolerance	115	63.9	101	45.3	144	70.2
Impaired glucose tolerance	34	18.9	69	30.9	20	9.8
Diabetes mellitus – newly diagnosed	15	8.3	24	10.8	14	6.8
Diabetes mellitus – known	16	8.9	29	13.0	27	13.2
Treatment: tablets	9		13		18	
insulin	1		4		4	
diet only	6		13		5	
Total	180		223		205	

Table 2. Selected characteristics of participating men aged 70–89 years at the 30-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study (1989/1990)

	east Finland ($n = 180$)		west Finland ($n = 223$)		Zutphen (NL) ($n = 205$)	
	Mean	SD	Mean	SD	Mean	SD
Age[a] (years)	74.9	1.1	76.0	1.1	75.8	1.1[b]
Body mass index (kg/m^2)	26.1	3.4	26.7	4.0	25.6	3.2[c]
Fasting insulin[a] (mU/l)	8.6	1.8	9.9	1.8	9.1	1.6
Total cholesterol (mmol/l)	5.8	1.2	5.7	1.1	6.1	1.1[d]
HDL cholesterol (mmol/l)	1.13	1.31	1.10	1.29	1.08	1.31
Fasting triglycerides[a] (mmol/l)	1.3	1.5	1.4	1.5	1.4	1.6
Systolic blood pressure[a] (mm Hg)	152	1.2	158	1.1	151	1.1[d]
Diastolic blood pressure[a] (mm Hg)	82	1.1	86	1.1	82	1.1[d]
Hypertension (%)	51.1		59.0		44.8	[b]

[a] geometric means; [b] $p < 0.05$; [c] $p < 0.01$; [d] $p < 0.001$

ered to have a mild form of diabetes and were therefore included, leaving 545 men for the hyperinsulinaemia analyses.

Mean values of selected characteristics were compared between the participating cohorts. When comparing risk factor levels according to glucose tolerance or hyperinsulinaemic status, analysis of covariance was used to adjust for confounders such as age, cohort and BMI. In case of skewed variables the geometric means were presented, based on logarithmic transformations. Logistic regression analysis was used to investigate the associations of glucose tolerance and hyperinsulinaemia with hypertension. A dummy variable for cohort was used as a covariate in all analyses to adjust for, e.g., differences in measurement methods such as for blood pressure and cultural or genetic differences. No interaction with cohorts was observed, as judged from analyses of covariance on repeated measurements, and associations between risk factors were essentially the same within each cohort. Therefore, only pooled results were presented. All *p*-values were based on two-sided tests of statistical significance.

Results

At the 30-year follow-up examination, the prevalence of clinically diagnosed diabetes varied from 8.9 % in east Finland to 13.2 % in Zutphen (Table 1). Another 8.7 % of the total study population was found to have newly-diagnosed diabetes after the GTT. The combined prevalence of diabetes and/or impaired glucose tolerance was highest in the cohort of west Finland (55 %), and significantly lower in east Finland and in the Netherlands. Men in west Finland were on average older and had higher mean BMI, blood pressure, glucose and insulin levels than the other cohorts (Table 2). Men from Zutphen had the highest total cholesterol level.

Cross-sectionally, no difference was observed in mean age between the categories of glucose tolerance (Table 3). The prevalence of hypertension, antihypertensive medication and means of BMI, blood pressure and fasting triglycerides were lower in men with normal glucose tolerance, also after adjusting for age and cohort. HDL-cholesterol levels were significantly higher. For most of these risk factors men with impaired glucose tolerance resembled those with diabetes.

The difference in the prevalence of hypertension at the 30-year follow-up between the categories of glucose tolerance could not be explained by BMI and fasting insulin, and persisted after excluding men using antihypertensive medication (Table 4).

During the entire 30-year period preceding the current GTT a significantly higher BMI was found in those men compared with men with normal glucose tolerance (Fig. 1). There was a similar tendency for systolic blood pressure (Fig. 2). Men with normal glucose tolerance at the 30-year follow-up had the lowest blood pressure level at all examinations. At each ex-

Table 3. Adjusted[a] mean characteristics according to glucose tolerance in men aged 70–89 years at the 30-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study (1989/1990)

	Normal glucose tolerance ($n = 360$)	Impaired glucose tolerance ($n = 123$)	Diabetes[b] ($n = 116$)
Age[c] (years)	75.4	75.9	76.1
Body mass index (kg/m^2)	25.8	26.6	26.8[d]
Fasting insulin[c] (mU/l)	8.2	10.0	12.1[f]
Total cholesterol (mmol/l)	5.9	5.7	5.7
HDL cholesterol (mmol/l)	1.13	1.06	1.06[d]
Fasting triglycerides[c] (mmol/l)	1.3	1.5	1.5[e]
Systolic blood pressure[c] (mm Hg)	151	157	159[f]
Diastolic blood pressure[c] (mm Hg)	82	85	85
Hypertension (%)	43.0	66.0	61.6[f]
Antihypertensive medication (%)	15.9	25.6	28.7[e]

[a] Adjusted for age and cohort by analysis of covariance; [b] patients treated for diabetes mellitus ($n = 68$, excluding those with insulin treatment) and newly-diagnosed diabetes ($n = 52$); [c] geometric means; [d] $p < 0.05$; [e] $p < 0.01$; [f] $p < 0.001$

Table 4. Adjusted odds ratios for the association between glucose tolerance and hypertension in men aged 70–89 years at the 30-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study (1989/1990)

	Normal glucose tolerance	Impaired glucose tolerance	Diabetes
Hypertension (%)	43.0	66.0	61.6
Odds ratios			
Adjusted for age, cohort, BMI	1.00	2.33 (1.51–3.58)[a]	2.18 (1.40–3.38)
and fasting insulin	1.00	2.25 (1.46–3.49)	2.27 (1.42–3.65)
excluding antihypertensive drug use	1.00	2.36 (1.46–3.81)	2.12 (1.24–3.61)

[a] 95 % confidence interval

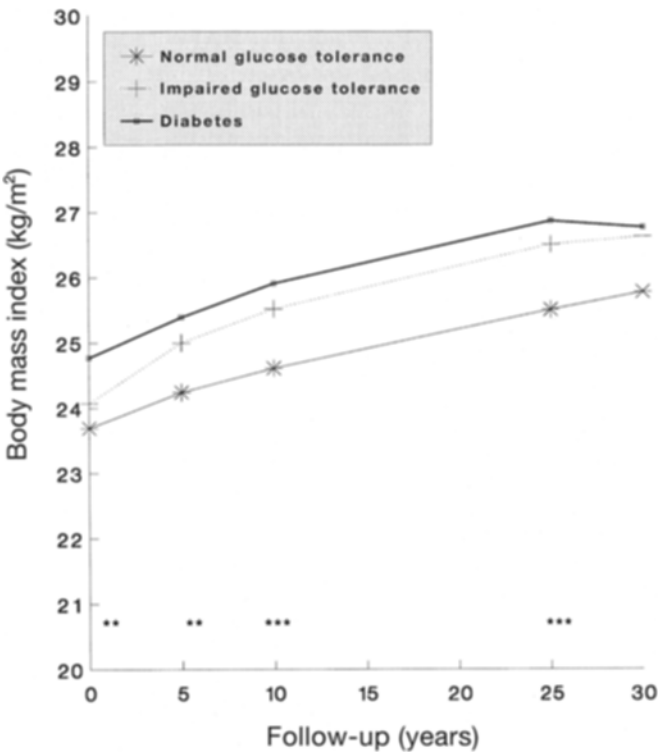

Fig. 1. Trends in body mass index during follow-up according to glucose tolerance status at the 30-year follow-up, adjusted for age and cohort by analysis of covariance. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

amination during the follow-up the differences were independent of age and cohort, and also independent of concomitant BMI ($p < 0.01$). Differences in diastolic blood pressure were smaller and not statistically significant after adjustment for BMI.

To study correlates of hyperinsulinaemia, men treated for diabetes were excluded from the study population. Men with hyperinsulinaemia (fasting serum insulin 9.2 mU/l or more) had significantly higher BMI, fasting triglycerides, diastolic blood pressure, prevalence of hypertension and antihypertensive medication, and significantly lower HDL-cholesterol at the 30-year follow-up (Table 5). The correlation between fasting insulin and 2-h glucose levels was 0.26, and with BMI was 0.46.

The elevated prevalence of hypertension among men with hyperinsulinaemia persisted after adjusting for BMI, but became borderline significant when the 2-h glucose levels were taken into account (Table 6). The result was essentially similar when men with antihypertensive treatment were excluded ($p = 0.10$). Stratified analyses showed that hyperinsulinaemia was positively associated with hypertension in lean men with normal glucose tolerance, in overweight men with normal glucose tolerance and in men with abnormal glucose tolerance, although the results were only borderline significant. The interaction term was not statistically significant ($p > 0.30$), indicating that the odds ratios in the subgroups were essentially similar.

Among men with hyperinsulinaemia, BMI was already high 30 years before the current insulin measurement (Fig. 3). Despite these large differences in BMI, no significant difference in systolic blood pres-

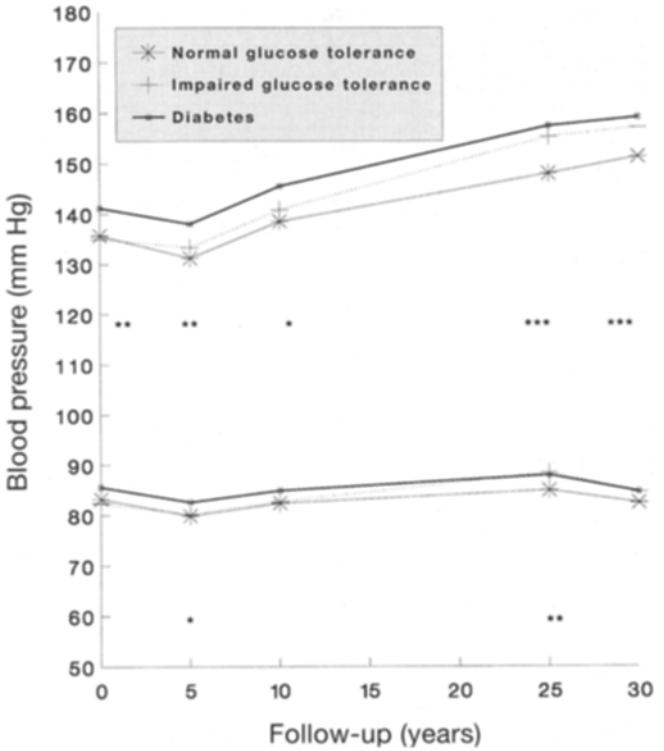

Fig. 2. Trends in blood pressure levels during follow-up according to glucose tolerance status at the 30-year follow-up, adjusted for age and cohort by analysis of covariance. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

sure was seen between men with and without hyperinsulinaemia (Fig. 4) ($p > 0.10$). In diastolic blood pressure the largest difference was observed at the 30-year follow-up measurement ($p < 0.01$). However, the differences in diastolic blood pressure between men with and without hyperinsulinaemia disappeared after adjustment for concurrent BMI ($p > 0.05$).

Discussion

The present study shows that glucose tolerance and hyperinsulinaemia are independently associated with hypertension and overweight in elderly men. In men with impaired glucose tolerance and diabetes, BMI and blood pressure were high 30 years before the current GTT. Among non-diabetic men, hyperinsulinaemia was associated with high BMI during the 30-year period preceding the current GTT-measurement, but such an association was not seen for blood pressure.

Our study population consisted of members of an international longitudinal study on cardiovascular disease risk factors, the Seven Countries Study. The surveys were carried out according to a standardized protocol with small differences in measurement methods. Such differences in methods as well as underlying differences in cultural and genetic factors were taken into account, since all analyses were done adjusting for the cohort. We did not find any interaction with cohort, and associations between risk factors were essentially the same within each cohort. Thus, the cohorts were pooled in the analyses presented. There is some evidence for ethnic heterogeneity in the role of insulin as a determinant of hypertension. Insulin resistance was associated with blood pressure in Caucasians, but not in blacks or Pima Indians [24], although in another study of hypertension in blacks a positive association with insulin resistance was found [25]. The present cohorts all consisted of Caucasian men, and ethnic differences in

Table 5. Adjusted[a] mean characteristics according to hyperinsulinaema in men aged 70–89 years at the 30-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study (1989/1990)

	Hyperinsulinaemia[b]	
	No ($n = 286$)	Yes ($n = 259$)
Age[c] (years)	75.7	75.4
Body mass index (kg/m^2)	24.8	27.7[e]
Total cholesterol (mmol/l)	5.9	5.8
HDL cholesterol (mmol/l)	1.18	1.03[e]
Fasting triglycerides[c] (mmol/l)	1.2	1.6[e]
Systolic blood pressure[c] (mm Hg)	153	155
Diastolic blood pressure[c] (mm Hg)	82	85[d]
Hypertension (%)	44.7	58.6[d]
Antihypertensive medication	13.9	26.5[e]

[a] Adjusted for age and cohort by analysis of covariance; [b] fasting insulin ≥ 9.2 mU/l, patients on anti-diabetic drugs excluded; [c] geometric means; [d] $p < 0.01$; [e] $p < 0.001$

Table 6. Adjusted odds ratios for the association between hyperinsulinaemia and hypertension in men aged 70–89 years at the 30-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study (1989/1990)

	Odds ratio	95 % Confidence interval
All men ($n = 546$)		
Adjusted for age, cohort, BMI	1.66	1.14–2.41
and 2-h glucose	1.42	0.97–2.10
Excluding antihypertensive drug use ($n = 436$)		
Adjusted for age, cohort, BMI	1.43	0.93–2.20
BMI < 25 kg/m^2 and NGT ($n = 150$)		
Adjusted for age, cohort, BMI	1.50	0.68–3.31
BMI < 25 kg/m^2 and IGT or diabetes ($n = 203$)		
Adjusted for age, cohort, BMI	1.38	0.76–2.50
BMI $\geq$ 25 kg/m^2 or IGT or diabetes ($n = 193$)		
Adjusted for age, cohort, BMI	1.44	0.73–2.84

NGT, Normal glucose tolerance;
IGT, impaired glucose tolerance

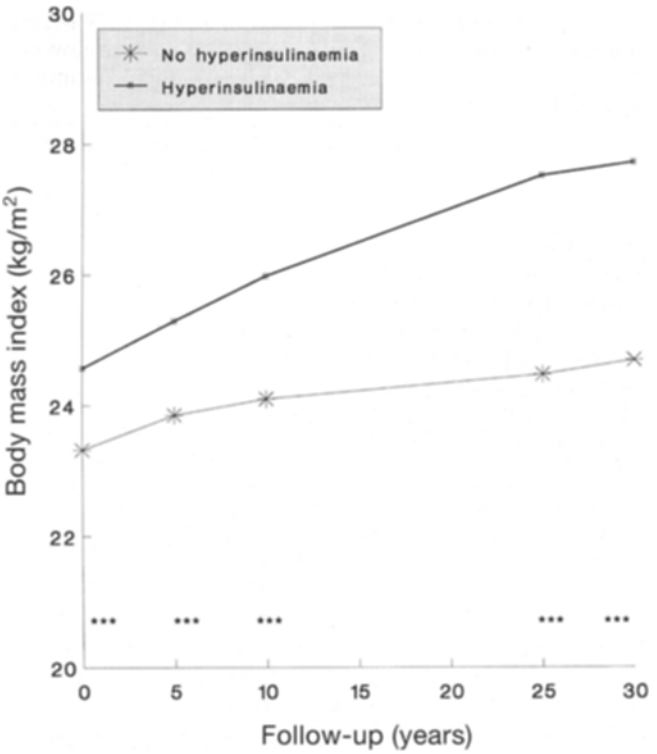

Fig. 3. Trends in body mass index during follow-up according to hyperinsulinaemia status at the 30-year follow-up, adjusted for age and cohort by analysis of covariance. *** $p < 0.001$

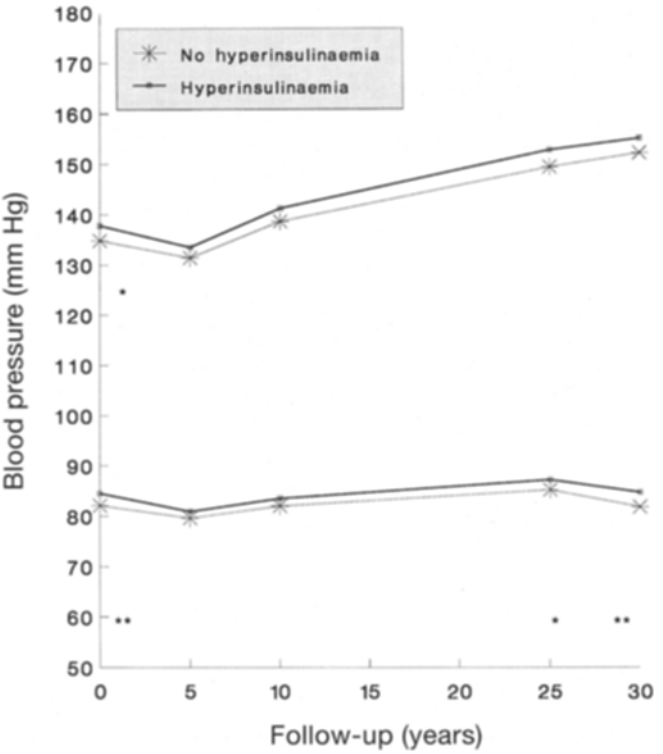

Fig. 4. Trends in blood pressure levels during follow-up according to hyperinsulinaemia status at the 30-year follow-up, adjusted for age and cohort by analysis of covariance. * $p < 0.05$; ** $p < 0.01$

this regard are probably small. Therefore, the cohorts were pooled, since this enhanced the range in variation of obesity, glucose intolerance and hyperinsulinaemia, and increased the power of the study.

The common characteristics among the participants of our study are that they had survived during the entire 30-year follow-up period, and reached the age of at least 70 years. For a study of hypertension, diabetes and hyperinsulinaemia this age group is very important because these conditions are most common among the elderly. Theoretically selection bias could have occurred, because of the survival of relatively healthy men. Since subjects with diabetes and hypertension may have increased mortality rates, men with this combination would especially have disappeared from our cohorts. This would have resulted in an attenuation of the association. However, the results show that associations of risk factors with glucose tolerance and hyperinsulinaemia, such as increased BMI and fasting serum triglycerides and decreased HDL-cholesterol, were similar as expected from studies among middle-aged subjects [1–5]. Bias may therefore be limited. In addition, it should be noted that selected survival is a common characteristic of any elderly person and thus of every epidemiological study on elderly subjects.

One of the main findings of this study is the positive cross-sectional association of hypertension with glucose tolerance and hyperinsulinaemia. The role of hyperinsulinaemia as an independent determinant of hypertension has been debated [6]. Insulin resistance has been found among lean hypertensive subjects in a number of studies [8–10], and hypertension is seen as an essential part of the insulin resistance syndrome ('X') [1–5]. Several mechanisms have been proposed to explain this observation, including effects on renal sodium absorption, cation transport, proliferation of vascular smooth muscle cells, and effects on the sympathetic nervous system [4]. Also effects by use of antihypertensive medication such as thiazides or beta-blockers could play a role [26]. However, epidemiologic population-based studies have produced conflicting results. Modan et al. [7] observed an association between post-load insulin levels and hypertension, independent of BMI, glucose intolerance, and antihypertensive medication. In contrast, studies of American elderly people of the Rancho Bernardo Study [12] and the Baltimore Study of Aging [13], and from several populations in the Pacific region [11], failed to confirm this observation. An association between fasting insulin and the risk of hypertension has been reported for Mexican Americans, but this association was not independent of BMI and skinfold ratio [5].

In the present study, the association between fasting insulin and hypertension remained after adjust-

ing for BMI. No data on fat distribution over the body were available on these men, but it can be assumed that additional adjustment for, e.g., waist-hip ratio would have reduced the association to some extent [27]. The interpretation of such adjusted association, however, remains unclear. By definition, confounding variables are those that are associated with the outcome independent of the exposure [28]. If the effect of body fat or fat distribution on hypertension would solely work via insulin, adjustment for these variables would therefore not be appropriate. Since the pathway is not yet fully elucidated [29], adjustment for body fat and fat distribution seems justified, but one should note that it may also include a certain amount of overadjustment.

Additional analyses showed that the effect was largely reduced when the 2-h blood glucose levels were taken into account, as also found by others [7, 11, 12]. The adjustment for post-load glucose which correlates with hyperinsulinaemia may introduce a multicollinearity problem in the multivariate analyses. In addition, blood glucose and insulin concentrations are strongly aetiologically related. It is generally assumed that insulin resistance and hyperinsulinaemia are the main underlying metabolic determinants for glucose intolerance and NIDDM [1–5]. Therefore, adjustment for post-load glucose may be inappropriate when studying the association between hypertension and hyperinsulinaemia.

An analysis in which the association between insulin and hypertension is investigated in groups of subjects stratified by body weight and glucose tolerance status, is a better approach. This is suggested also by results from a Finnish study, in which lean diabetic patients with hypertension were more insulin resistant than lean diabetic patients without hypertension, but that this difference according to hypertension was not seen among the obese diabetic patients [10]. In the prospective study among Mexican Americans fasting insulin was independently associated with risk of hypertension in the lean population with normal glucose tolerance [5]. Among hypertensive patients insulin resistance was especially reported among the lean ones [8]. However, others reported an association between hyperinsulinaemia and hypertension in obese subjects only [30, 31], or in diabetic subjects [10, 32]. When we restricted our analyses to lean men with normal glucose tolerance or to men with either overweight or abnormal glucose tolerance the results were only borderline significant, but also not essentially different from those of the entire study population. This indicates that susceptible subgroups could not be clearly discerned in our population-based cohorts.

We observed a stronger association between hypertension and glucose tolerance than between hypertension and hyperinsulinaemia. Men with abnormal glucose tolerance had higher blood pressure levels already 30 years preceding the GTT, whereas hyperinsulinaemia was not clearly associated with earlier blood pressure measurements. Although past measurements of BMI were higher in men with abnormal glucose tolerance, these could not explain the blood pressure results. Differences in systolic blood pressure were marked, and men with newly-diagnosed diabetes and impaired glucose tolerance had the largest blood pressure increase during the 30-year study. One of the explanatory factors could be antihypertensive medication. Thiazides and beta-blockers can have diabetogenic effects [26]. Such an effect was not seen among Mexican Americans [14], and also other studies suggest that the effect of these drugs is probably small [10, 33]. To control for the possible effect of antihypertensive medication at the 30-year follow-up survey we excluded current drug users from the analyses, and our results remained essentially unchanged. In addition, during the first 10 years of our study the use of antihypertensive drugs was uncommon.

However, for the analysis of insulin exclusion of men using antihypertensive drugs resulted in a smaller odds ratio (1.66 vs 1.43), which was only borderline significant. This suggests that the higher prevalence of hyperinsulinaemia in hypertensive patients is due to the use of diuretics and beta-blockers. However, this observation may also partly be a statistical artifact due to the reduction of study power and excluding the more severe cases of hypertension. Irrespective of the underlying explanation, this confirms that the association with hypertension is stronger for glucose tolerance than for hyperinsulinaemia.

Other investigators have also reported a stronger association between hypertension and glucose tolerance rather than between hypertension and hyperinsulinaemia [14, 34]. An explanation for this finding has not been found. One possibility is the longer duration of the insulin resistance present in men with impaired glucose tolerance or diabetes, and a possible higher prevalence of additional vascular problems [35, 36]. One interesting finding in this respect may be that glucose tolerance was mainly associated with systolic blood pressure, whereas the strongest association for hyperinsulinaemia was seen with the diastolic blood pressure. This has been reported previously [30], and suggests that glucose tolerance is associated with cardiac output and compliance of the macrovascular system, whereas hyperinsulinaemia is more strongly related to systemic vascular resistance and haemodynamic mechanisms [37]. This difference requires further attention. Finally, it is also possible that diabetes and hypertension are linked by some other genetic or environmental determinant than hyperinsulinaemia and hypertension, which remains to be identified.

The observed associations of glucose tolerance and hyperinsulinaemia with overweight were as expected. Nevertheless, our finding that these differ-

ences could already be seen 30 years earlier has an important public health message. It stresses the need for prevention of overweight in preventing derangements in glucose metabolism in old age.

In conclusion, both abnormal glucose tolerance and hyperinsulinaemia are associated with hypertension and blood pressure, but the relationship with glucose tolerance was stronger. Also, past blood pressure measurements were associated with abnormal glucose tolerance, but not hyperinsulinaemia. This may be partly explained by the fact that men with impaired glucose tolerance and diabetes may have had insulin resistance present for a long time. Since previous blood pressure levels did not predict hyperinsulinaemia it cannot be excluded that insulin may be the underlying metabolic risk factor for both abnormal glucose tolerance and hypertension. Hyperinsulinaemia and hypertension may both be part of a complex of metabolic risk factors, with both genetic and environmental determinants. This needs to be confirmed by further longitudinal studies, including repeated insulin measurements. The relative weakness of the association between hyperinsulinaemia and hypertension, and the inconsistent results of studies among various populations, however, still warrant caution about the causality of this association.

Acknowledgements. This study was supported by grants from the National Institute on Aging, USA (grant number EDC-1 1 RO1 AG08762-O1A1), the Preaventiefonds, The Netherlands, the Medical Research Council, Finland, and the Sandoz Gerontological Foundation. Dr. Feskens was supported by grants from the Academy of Science of Finland and the Netherlands Organization for Scientific Research. We are indebted to the many people involved in this longitudinal study, including all participants and the fieldwork teams in east and west Finland and in Zutphen. We thank the Laboratory of Clinical Chemistry and Haematology of the Nieuwe Spitaal hospital in Zutphen for the glucose analyses, and the Laboratory of the Unit of Teratology, Endocrinology and Perinatal Screening of the RIVM (Dr. J. G. Loeber and Mr. L. Elvers) and Dr. A. Julkunen (University of Kuopio) for the analyses of serum insulin.

References

1. Reaven GM (1988) Banting lecture 1988: role of insulin resistance in human disease. 37: 335–344
2. Björntorp P (1988) The associations between obesity, adipose tissue distribution and disease. Acta Med Scand [Suppl 723]: 121–134
3. Kaplan NM (1989) The deadly quartet: upper-body adiposity, glucose intolerance, hypertriglyceridemia and hypertension. Arch Intern Med 149: 1514–1520
4. DeFronzo RA, Ferrannini E (1991) Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care 14: 173–194
5. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP (1992) Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 41: 715–722
6. Donahue RP, Skyler JS, Schneiderman B, Prineas RJ (1990) Hyperinsulinemia and elevated blood pressure: cause, confounder, or coincidence? Am J Epidemiol 132: 827–836
7. Modan M, Halkin H, Almog S et al. (1985) Hyperinsulinemia: a link between hypertension, obesity and glucose intolerance. J Clin Invest 75: 807–817
8. Ferrannini E, Buzzigioli G, Bonadonna R et al. (1987) Insulin resistance in essential hypertension. N Engl J Med 317: 350–357
9. Zavaroni I, Bonora E, Pagliara M et al. (1989) Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 320: 702–706
10. Laakso M, Sarlund H, Mykkänen L (1989) Essential hypertension and insulin resistance in non-insulin-dependent diabetes. Eur J Clin Invest 19: 518–526
11. Collins VR, Dowse GK, Finch CF, Zimmet PZ (1990) An inconsistent relationship between insulin and blood pressure in three Pacific Island populations. J Clin Epidemiol 43: 1369–1378
12. Asch S, Wingard DL, Barrett-Connor EL (1991) Are insulin and hypertension independently related? Ann Epidemiol 1: 231–244
13. Muller DC, Elahi D, Pratley RE, Tobin JD, Andres R (1993) An epidemiological test of the hyperinsulinemia-hypertension hypothesis. J Clin Endocrinol Metab 76: 544–548
14. Morales PA, Mitchell BD, Valdez RA, Hazuda HP, Stern MP, Haffner SM (1993) Incidence of NIDDM and impaired glucose tolerance in hypertensive subjects. Diabetes 42: 154–161
15. Keys A (1970) Coronary heart disease in seven countries. Circulation 41 [Suppl 1]: 1–211
16. Keys A, Aravanis C, Blackburn HW et al. (1967) Epidemiological studies related to coronary heart disease: characteristics of men aged 40–59 in seven countries. Acta Med Scand 460 [Suppl 1]: 1–392
17. World Health Organization (1985) Diabetes Mellitus. Report of a WHO Study Group. WHO Technical Report Series no. 727. Geneva
18. World Health Organization (1978) Arterial hypertension. Technical Report Series no. 628. Geneva
19. Siedel J, Schlumberger H, Klose S, Ziegenhorn J, Wahlefeld AW (1981) Improved reagent for the enzymatic determination of serum cholesterol. J Clin Chem Clin Biochem 19: 838–839
20. Sullivan DR, Kruijswijk Z, West CE, Kohlmeier M, Katan MB (1985) Determination of serum triglycerides by an enzymatic method not affected by free glycerol. Clin Chem 31: 1227–1228
21. Warnick GR, Benderson J, Albers JJ (1982) Dextran sulfate-Mg^{2+} precipitation procedure for quantification of high-density-lipoprotein cholesterol. Clin Chem 28: 1379–1388
22. Rose GA, Blackburn H (1968) Cardiovascular survey methods. Geneva, World Health Organization
23. SAS Institute (1985) SAS user's guide: statistics. SAS Institute Inc., Cary
24. Saad MF, Lillioja S, Swinburn B et al. (1991) Racial differences between blood pressure and insulin resistance. N Engl J Med 324: 733–739
25. Falkner B, Hulman D, Tannebaum J, Kushner H (1990) Insulin resistance and blood pressure in young black men. Hypertension 16: 706–711
26. Lithell HOL (1991) Effect of antihypertensive drugs on insulin, glucose and lipid metabolism. Diabetes Care 14: 203–209

27. Jarrett JR (1992) In defence of insulin: a critique of syndrome X. Lancet 340: 469–471
28. Weinberg CR (1993) Toward a clearer definition of confounding. Am J Epidemiol 137: 1–8
29. Alderman MH (1994) Non-pharmacological treatment of hypertension. Lancet 344: 307–311
30. Christlieb AR, Krolewski AS, Warram JH, Soeldner JS (1985) Is there a link between hypertension and obesity? Hypertension 7 [Suppl 2]: 54–57
31. Wing RR, Bunker CH, Kuller LH, Matthews KA (1989) Insulin, body mass index, and cardiovascular risk factors in premenopausal women. Arteriosclerosis 9: 479–484
32. Mbanya JN, Thomas TH, Wilkinson R, Alberti KGMM, Taylor R (1988) Hypertension and hyperinsulinaemia: a relation in diabetes but not essential hypertension. Lancet I: 733–734
33. Amery A, Brixko R, Clement D et al. (1986) Efficacy of antihypertensive drug treatment according to age, sex, blood pressure, and previous cardiovascular disease in patients over the age of 60. Lancet II: 589–592
34. Cambien F, Warnet JM, Eschwege E, Jacqueson A, Richard JL, Rosselin G (1987) Body mass, blood pressure, glucose and lipids – does plasma insulin explain their relationships? Arteriosclerosis 7: 197–202
35. Pan WH, Cedres LB, Liu K et al. (1986) Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. Am J Epidemiol 123: 504–516
36. Feskens EJM, Kromhout D (1992) Glucose tolerance and the risk of cardiovascular diseases: the Zutphen Study. J Clin Epidemiol 45: 1327–1334
37. Feldman RD, Bierbier GS (1993) Insulin-mediated vasodilation: impairment with increased blood pressure and body mass. Lancet 342: 707–709