

Hyperinsulinemia Is Associated With the Incidence of Hypertension and Dyslipidemia in Middle-Aged Men

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Insulin resistance or compensatory hyperinsulinemia has been associated with hypertension and dyslipidemia in cross-sectional studies. In contrast, evidence from prospective population-based studies, which could establish the time order of the relationship, is sparse and inconsistent. Therefore, we investigated the associations of hyperinsulinemia with the incidence of hypertension and dyslipidemia in the Kuopio Ischemic Heart Disease Risk Factor Study, a population-based 4-year follow-up study of middle-aged men from eastern Finland. Out of 975 men who had no diabetes, 543 had resting systolic blood pressure (sBP) of <165 mmHg and resting diastolic blood pressure (dBP) of <95 mmHg at baseline and were not taking antihypertensive medication, and 764 had serum triglycerides of <2.3 mmol/l and HDL cholesterol of ≥ 1.0 mmol/l at baseline. In logistic regression models adjusted for age, baseline resting blood pressure, baseline lipids, obesity, weight change, and other risk factors, men with hyperinsulinemia (fasting insulin in the highest quintile, ≥ 12.0 mU/l) at baseline had a 2.0-fold (95% CI 1.1–3.5, $P = 0.025$) incidence of hypertension (sBP of ≥ 165 or dBP of ≥ 95 mmHg), a 2.1-fold (95% CI 1.3–3.4, $P = 0.002$) incidence of dyslipidemia (serum HDL cholesterol of <1.0 mmol/l or serum triglycerides of ≥ 2.3 mmol/l), and a 2.6-fold (95% CI 1.1–6.3, $P = 0.028$) incidence of the combination of these disorders in 4 years, compared with normoinsulinemic men. These findings demonstrate the role of hyperinsulinemia in incident hypertension and dyslipidemia and suggest that both hypertension and dyslipidemia are associated with insulin metabolism disturbance, independently of obesity and body weight. *Diabetes* 47:270–275, 1998

Insulin resistance or compensatory hyperinsulinemia has been associated with hypertension in a number of cross-sectional studies (1,2). In some studies, the association has been independent of obesity and glucose intolerance (3,4). However, in other studies, the relationship has been explained by obesity, glucose intolerance, or anti-

hypertensive medication (5–7), or there have been large racial differences (8). Insulin resistance or hyperinsulinemia has been consistently associated with hypertriglyceridemia and a decreased serum HDL cholesterol level in cross-sectional studies (1,2). Experimental studies have provided some further evidence for the role of insulin resistance in the etiology of hypertension (9) and dyslipidemia (10). There are several pathophysiological pathways through which hyperinsulinemia could elevate blood pressure (11) and cause dyslipidemia (2,12).

Reaven (1,13) hypothesized the existence of a syndrome, in which insulin resistance is the primary defect, that is characterized by hyperinsulinemia, glucose intolerance, hypertriglyceridemia, a decreased serum HDL cholesterol level, and hypertension, which he called syndrome X. Recently, this cluster of cardiovascular risk factors has been most frequently referred to as insulin resistance syndrome (2,14). Evidence in favor of the hypothesis implicating insulin resistance and hyperinsulinemia in the etiology of hypertension and dyslipidemia and the concept of insulin resistance syndrome derives mainly from cross-sectional studies, on the basis of which it is impossible to conclude whether insulin resistance is a cause of hypertension and dyslipidemia or a consequence of these disorders. In contrast, evidence from prospective population-based studies, which could establish the time order of the relationship, is sparse and inconsistent. Hyperinsulinemia has been associated with increased incidence of hypertension independently of obesity in men (15) and women (16). In other studies, however, hyperinsulinemia has predicted hypertension in only selected population groups, such as in nondiabetic normotensive non-Hispanic whites (17) and lean normoglycemic people (14). Hyperinsulinemia was independently associated with the development of lipid and lipoprotein abnormalities in one study (14), whereas these relationships were largely explained by obesity in another study (18).

The purpose of this study is to test the hypothesis that insulin resistance, as indicated by elevated fasting serum insulin levels, increases the incidence of hypertension and dyslipidemia and the combination of these disorders in an unselected population of middle-aged men and does so independently of obesity, body weight, and other potentially relevant confounders.

RESEARCH DESIGN AND METHODS

Study population. The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) is an ongoing population-based study designed to investigate previously unestablished risk factors for cardiovascular diseases and carotid atherosclerosis in middle-aged men from the Kuopio region in Eastern Finland (19), an area with a high occurrence of cardiovascular diseases (20). A total of 2,682 partici-

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dBP, diastolic blood pressure; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study; RR, relative risk; sBP, systolic blood pressure; WHR, waist-to-hip ratio.

participants (82.9% of those eligible), aged 42, 48, 54, or 60 years, were enrolled in the study between March 1984 and December 1989. Follow-up examinations were conducted between March 1991 and December 1993 on those men who had undergone ultrasound examination of the right and left carotid arteries at baseline. A total of 1,229 men were eligible for the follow-up study; of these, 52 had died, were suffering severe illness, or had migrated away from the region, and 139 could not be contacted or refused to participate. Thus, the follow-up study included 1,038 participants or 88.2% of those eligible. Average time to follow-up was 4.1 years (range 3.8–5.2 years).

For all analyses, subjects were excluded if they had missing values on blood glucose, serum insulin, or blood pressure at baseline or follow-up ($n = 22$) or had diabetes ($n = 41$), resulting in a final sample of 975 men. Diabetes was defined as either a fasting blood glucose of ≥ 6.7 mmol/l or a clinical diagnosis of diabetes with dietary, oral, or insulin treatment. In the analyses of incident hypertension, 455 men who were hypertensive (systolic blood pressure [sBP] of ≥ 165 mmHg, diastolic blood pressure [dBP] of ≥ 95 mmHg, or taking antihypertensive medication) at baseline were excluded, leaving a sample of 543 initially normotensive men. For the analyses of incident dyslipidemia (serum HDL cholesterol of < 1.0 mmol/l or serum triglycerides of ≥ 2.3 mmol/l), we excluded men who had either missing values in serum HDL cholesterol or triglycerides at baseline or follow-up ($n = 15$) or dyslipidemia ($n = 214$) at baseline, resulting in a sample of 764 initially normolipidemic men. In the analyses of the occurrence of the combination of hypertension and dyslipidemia, both initially hypertensive dyslipidemic men and those with missing values in blood pressure, serum HDL cholesterol, or triglycerides were excluded, resulting in a sample of 452 initially normotensive and normolipidemic men.

Baseline and follow-up examinations. Examinations were carried out over 2 days, 1 week apart, at both baseline and follow-up, and consisted of a wide variety of biochemical, physiological, anthropometric, and psychosocial measures. Medical history and medication use were checked during a medical examination at both baseline and follow-up.

Blood sampling. The subjects gave blood specimens between 8:00 and 10:00 A.M. on Tuesday, Wednesday, or Thursday. They were instructed to fast and to abstain from smoking for 12 h and to abstain from drinking alcohol for 3 days. After the subjects had rested in the supine position for 30 min, blood was drawn with a Terumo Venoject VT-100PZ vacuum (Tokyo, Japan). No tourniquet was used.

Measurement of serum insulin and blood glucose and definition of hyperinsulinemia. Serum insulin was measured with a radioimmunoassay (Novo Nordisk, Bagsvaerd, Denmark). Hyperinsulinemia was arbitrarily defined as fasting serum insulin of ≥ 12.0 mU/l, the highest fifth of the baseline distribution of serum insulin among both the nondiabetic normotensive ($n = 543$) and the nondiabetic normolipidemic ($n = 764$) subjects. Blood glucose was measured using a glucose dehydrogenase method (Merck, Darmstadt, Germany) after precipitation of proteins by trichloroacetic acid.

Measurement of blood pressure and definition of hypertension. The blood pressure data used in the present analyses were obtained on two occasions by a trained observer using a random-zero muddler sphygmomanometer (Hawksley, London, U.K.). The blood pressure measurement protocol on the first examination day was as follows: 15-min supine rest with blood pressure measured at 5, 10, and 15 min; standing rest with one blood pressure reading taken after 1 min; 10-min seated rest with blood pressure measured at 5 and 10 min. For the present analyses, the averages of the two seated measurements were considered resting sBP and dBP. Measurements occurred in the mornings. The blood pressure measurement protocol at follow-up was identical to the baseline protocol. A subject was considered to be hypertensive at the 4-year follow-up examination if his resting sBP was ≥ 165 mmHg, his resting dBP was ≥ 95 mmHg, or if he was currently taking antihypertensive medication (21).

Assessment and definition of dyslipidemia. The main lipoprotein fractions (HDL, LDL, VLDL) were separated from fresh serum samples using precipitation and ultracentrifugation (22). The cholesterol contents of lipoprotein fractions were measured enzymatically (CHOD-PAP cholesterol method, Boehringer Mannheim, Mannheim, Germany) on the day after the last ultracentrifugal spin. Serum triglycerides were also measured enzymatically (GPO-PAP triglycerides method, Boehringer Mannheim). Dyslipidemia was defined as serum HDL cholesterol of < 1.0 mmol/l or serum triglycerides of ≥ 2.3 mmol/l, according to the European guidelines for the treatment of dyslipidemia (23). The dyslipidemia measurement protocol at follow-up was identical to the baseline protocol.

Assessment of confounding factors. Assessment of medical history, family history of diseases, and laboratory measurements (19,21,22,24–28) have been described elsewhere. BMI was computed as the ratio of weight to the square of height, and waist-to-hip ratio (WHR) was computed as the ratio of the circumference of the waist to the hip. Because an earlier study of KIHJ participants showed that the proportion of saturated fatty acids of all serum fatty acids was associated with the incidence of diabetes (26), that variable also was included as a covariate in all statistical models.

Statistical methods. Differences between hyperinsulinemic and normoinsulinemic subjects in baseline characteristics and in the incidence of hypertension, dyslipidemia, and the combination of these were analyzed using Student's *t* tests. The linear trend in the incidence of these outcomes over the quintiles of the baseline insulin distribution was tested with the Mantel's extension of the Mantel-Haenszel test. The adjusted (partial) associations of baseline fasting serum insulin levels with the incidence of hypertension, dyslipidemia, and their combination were estimated and tested for significance using multivariate logistic regression analysis. The risk of developing these conditions during the 4-year follow-up was predicted by the presence of hyperinsulinemia at baseline. All statistical analyses were conducted with LOGISTIC and GLM procedures from SAS, version 6.09, installed on an IBM RS/6000.

RESULTS

Among all 975 subjects, the baseline fasting serum insulin had a mean of 10.5, median of 9.3, SD of 5.7, minimum of 1.0, and maximum of 50.0 mU/l. The baseline characteristics of all 975 men are shown separately for the hyperinsulinemic and normoinsulinemic subjects in Table 1. Expectedly, baseline levels of insulin, glucose, triglycerides, blood pressure, and indicators of obesity were higher and serum HDL cholesterol lower among hyperinsulinemic than normoinsulinemic subjects. Also, prevalences of conditions related to genetic predisposition to insulin resistance, e.g., history of hypertension in parents and in siblings and being overweight in mother, were higher in hyperinsulinemic men. The proportion of saturated fatty acids of all serum fatty acids was also higher among the hyperinsulinemic subjects. There was no significant difference in weight change during the 4-year follow-up.

Of the 543 initially normotensive men, 123 (22.7%) developed hypertension during the follow-up. Of the 764 men who were normolipidemic at baseline, 258 (33.8%) had dyslipidemia 4 years later. The unadjusted cumulative incidence of hypertension was 2.0-fold in the hyperinsulinemic compared with the normoinsulinemic subjects ($P < 0.001$ for difference, Table 1). The respective incidence of dyslipidemia was 1.8-fold ($P < 0.001$) and that of the combination of both these disorders 3.5-fold ($P < 0.001$) in the initially hyperinsulinemic men, as compared with normoinsulinemic men (Table 1).

The unadjusted cumulative incidence of the combination of hypertension and dyslipidemia was 5.3, 8.9, 0.0, 10.1, and 21.6% in the fifths (≤ 6.1 , 6.2–7.5, 7.6–9.3, 9.4–11.9, and 12.0+ mU/l) of the baseline insulin distribution ($n = 452$, $P = 0.0010$ for linear trend). The respective incidence rates were 20.6, 15.7, 15.5, 23.6, and 38.1% for hypertension ($P = 0.0005$ for linear trend) and 21.9, 27.3, 28.8, 35.2, and 52.8% for dyslipidemia ($P < 0.0001$ for linear trend). There was no consistent association below the highest quintile of baseline fasting insulin (12.0 mU/l).

In logistic models including age, examination years, and each additional risk factor one by one, the strongest risk factors for incident hypertension in 543 normotensive men were mean blood pressure at baseline, BMI, hyperinsulinemia ($P < 0.001$), serum triglycerides ($P = 0.001$), hypertension in siblings ($P = 0.005$), history of being overweight in mother ($P = 0.007$), WHR ($P = 0.01$), and the change in weight during follow-up ($P = 0.03$). Those for incident dyslipidemia in 764 normolipidemic men were serum triglycerides, serum HDL cholesterol, WHR, BMI, the change in weight during follow-up, the proportion of saturated of all serum fatty acids, hyperinsulinemia ($P < 0.001$), blood leukocytes ($P = 0.004$), lipid-standardized serum α -tocopherol ($P = 0.03$), and mean blood pressure at baseline ($P = 0.05$). The use of either β -

TABLE 1

Distributions of potential confounding factors at baseline ($n = 975$) and the incidence of hypertension, dyslipidemia, and the combination of these disorders among initially hyperinsulinemic and normoinsulinemic men

	Hyperinsulinemic men	Normoinsulinemic men	<i>P</i> values for difference in means
<i>n</i>	269	706	—
Age (years)	52.5 ± 6.8	51.7 ± 6.6	0.127
Fasting blood glucose (mmol/l)	4.76 ± 0.54	4.47 ± 0.45	<0.001
Fasting serum insulin (mU/l)	17.3 ± 6.4	8.0 ± 2.2	<0.001
sBP (mmHg)	135.6 ± 15.0	130.1 ± 15.6	<0.001
dBP (mmHg)	90.6 ± 9.7	86.3 ± 10.1	<0.001
Serum HDL cholesterol (mmol/l)	1.18 ± 0.25	1.35 ± 0.31	<0.001
Serum triglycerides (mmol/l)	1.89 ± 1.07	1.23 ± 0.65	<0.001
Hypertension in parents	45.7	41.6	0.250
Hypertension in siblings	27.4	20.8	0.020
Overweight in mother	42.1	36.6	0.112
Proportion of saturated of all serum fatty acids	0.53 ± 0.06	0.49 ± 0.05	<0.001
BMI (kg/m ²)	29.1 ± 3.5	25.8 ± 2.8	<0.001
WHR	0.97 ± 0.05	0.93 ± 0.06	<0.001
Four-year change of weight (kg)	2.04 ± 4.42	2.52 ± 3.94	0.103
Incidence of hypertension (among initially normotensive men)	38.1 (<i>n</i> = 113)	18.8 (<i>n</i> = 430)	<0.001
Incidence of dyslipidemia (among initially normolipidemic men)	52.8 (<i>n</i> = 161)	28.7 (<i>n</i> = 603)	<0.001
Incidence of the combination of both hypertension and dyslipidemia among initially normotensive and normolipidemic men	21.6 (<i>n</i> = 74)	6.1 (<i>n</i> = 378)	<0.001

Data are means ± SE or %. Hyperinsulinemia is defined as fasting serum insulin of ≥12.0 mU/l (in the highest fifth of distribution in normotensive men).

blocking agents, diuretics, or other antihypertensive agents at baseline had no significant association with dyslipidemia incidence. The start of any β -blocking agent during the follow-up was associated with a 2.9-fold age- and examination year-adjusted risk of incident dyslipidemia (95% CI 1.4–6.4, $P = 0.006$), whereas starting a diuretic had no significant association with dyslipidemia incidence. The most often used diuretic was hydrochlorothiazide, and its most frequent dose was 25 mg daily.

The strongest risk factors for the combination of incident hypertension and incident dyslipidemia in 452 men with neither of these conditions at baseline were serum triglycerides, serum HDL cholesterol, BMI, the change in weight during follow-up, hyperinsulinemia ($P < 0.001$), mean blood pressure at baseline ($P = 0.002$), and WHR ($P = 0.009$).

After adjustment for age, the year of examination, time of blood pressure measurements (h, min), history of hypertension in mother or father and, separately, in siblings, history of being overweight in mother, the proportion of saturated of all serum fatty acids, mean blood pressure (mean of two sBP and two dBP values), as well as serum triglycerides and HDL cholesterol, hyperinsulinemic men had a 2.0-fold (95% CI 1.1–3.4, $P = 0.017$) risk of incident hypertension, a 2.2-fold (95% CI 1.4–3.4, $P = 0.0003$) risk of subsequent dyslipidemia, and a 3.2-fold (95% CI 1.4–7.2, $P = 0.005$) risk of the combination of these disorders (Table 2). Of the initially normolipidemic men, 133 used antihypertensive medications at baseline (94 used β -blockers, 23 diuretics, and 33 other). An additional statistical adjustment (by using three indicator variables) for these medications did not influence the relative risk (RR) for incident dyslipidemia at all.

Serum insulin concentration as a continuous variable also had statistically significant independent associations with the risk of both incident hypertension ($P = 0.019$) and dyslipidemia ($P = 0.005$). For the combination of these, the association did not reach statistical significance. On the average, for a unit (mU/l) of serum insulin, the risk of hypertension increased by 6.0% (95% CI 1.0–11.2) and that of dyslipidemia by 5.8% (95% CI 1.7–10.0) (Table 2).

To separate out the effects of obesity and weight change, we also repeated all statistical analyses with an additional inclusion of BMI, WHR, and the 4-year change of weight into all multivariate models. After these additional adjustments, hyperinsulinemic men had a 2.0-fold (95% CI 1.1–3.5, $P = 0.025$) risk of hypertension, a 2.1-fold (95% CI 1.3–3.4, $P = 0.002$) risk of dyslipidemia, and a 2.6-fold (95% CI 1.1–6.3, $P = 0.028$) risk of the combination of these disorders (Table 3). Also, the associations of serum insulin concentration with the risk of hypertension and dyslipidemia remained statistically significant after the adjustment for obesity and weight change (Table 3). Entering of any variable concerning indicators of inflammation, medical history, prevalent diseases, nutrient intakes, cardiorespiratory fitness, physical activity, or socioeconomic factors, including adulthood socioeconomic status, income, and place of residence, into the models did not change the strength of the associations of hyperinsulinemia and serum insulin with the risk of hypertension and dyslipidemia. The cumulative incidence rates in the quintiles of baseline serum insulin, adjusted for the covariates used in Table 3, including BMI, WHR, the 4-year change of weight, and start of β -blocker or diuretic, were 9.6, 10.3, 0.3, 7.6, and 18.2% for the combination of hypertension and dyslipidemia

TABLE 2

Relative 4-year incidence of hypertension, dyslipidemia, and the combination of these disorders, associated with pre-follow-up hyperinsulinemia and serum insulin concentration, adjusted for other predictors, excluding obesity

	Incidence of hypertension (sBP of ≥ 165 mmHg or dBP of ≥ 95 mmHg)			Incidence of dyslipidemia (serum HDL cholesterol of <1.0 mmol/l or serum triglycerides of ≥ 2.3 mmol/l)			Incidence of the combination of hypertension and dyslipidemia		
	RR	95% CI	<i>P</i> value	RR	95% CI	<i>P</i> value	RR	95% CI	<i>P</i> value
Hyperinsulinemia at baseline	1.95	1.13–3.38	0.0170	2.21	1.44–3.41	0.0003	3.20	1.43–7.17	0.0046
Fasting serum insulin at baseline (mU/l)	1.06	1.01–1.11	0.0191	1.06	1.02–1.10	0.0052	1.07	0.99–1.16	0.1042

Hyperinsulinemia is defined as fasting serum insulin of ≥ 12.0 mU/l (in the highest fifth of distribution). All models include the following covariates: age, the year of examination, time (h, min) of blood pressure measurements, history of hypertension in mother or father and, separately, in siblings, history of being overweight in mother, proportion of saturated of all serum fatty acids, baseline mean blood pressure (mean of two sBP and two dBP values), and serum triglycerides and HDL cholesterol.

($P = 0.001$), 24.9, 18.2, 17.9, 21.6, and 31.3% for hypertension ($P = 0.081$), and 32.7, 31.3, 27.5, 30.7, and 43.7% for dyslipidemia ($P = 0.015$).

To analyze whether obesity modifies the effect of hyperinsulinemia on the incidence of hypertension and dyslipidemia, the logistic models with the same covariates were fitted separately among men below and above the median of BMI (25.2 kg/m^2). The RR of hypertension associated with hyperinsulinemia (serum insulin ≥ 12 mU/l) was similar in both groups, whereas that for serum insulin concentration tended to be greater (1.065, 95% CI 1.01–1.13, $P = 0.0332$) among the obese men ($n = 291$) than nonobese men (1.045, 95% CI 0.93–1.17, $P = 0.4628$; $n = 252$). The difference was, however, not statistically significant. For the incidence of dyslipidemia, the RRs for both hyperinsulinemia (2.1 and 2.3, respectively) and serum insulin concentration (1.05 for both) were identical among the obese and nonobese subjects.

DISCUSSION

To our knowledge, this is the first prospective study to investigate the independent associations of hyperinsulinemia with the risk of hypertension and dyslipidemia and the combination of these disorders in an unselected population of middle-aged men. Hyperinsulinemic men had a 2.0-fold incidence of hypertension, a 2.1-fold incidence of dyslipidemia, and a 2.6-fold incidence of the combination of these conditions during

a 4-year follow-up period compared with normoinsulinemic men after controlling for confounding factors, including obesity and body weight. The association was similar among the initially obese and nonobese subjects. This study provides strong evidence in favor of the hypothesis implicating insulin resistance in the etiology of hypertension and dyslipidemia and the concept of the insulin resistance syndrome. However, it is theoretically possible that determinants of hypertension and dyslipidemia are different in women. This remains to be discovered in further studies.

Even though the numbers of incident hypertension and dyslipidemia provided only a limited statistical power for analysis of dose-response relationships, there was some evidence of a threshold effect. Below the highest quintile of serum insulin (12.0 mU/l), serum insulin had no consistent relationship with the incidence of hypertension and only a weak relationship with the incidence of dyslipidemia.

The strongest evidence that insulin resistance contributes to the pathogenesis of hypertension and dyslipidemia derives from prospective population-based studies. Hyperinsulinemia has been associated with an increased incidence of hypertension independently of BMI in Swedish middle-aged men (15) and women (16). A high value of serum insulin area under the glucose tolerance curve was related to an increase in sBP in nondiabetic normotensive non-Hispanic, but not in Hispanic, white Colorado residents (17). Hyperinsulinemia

TABLE 3

Relative 4-year incidence of hypertension, dyslipidemia, and the combination of these disorders associated with pre-follow-up hyperinsulinemia and serum insulin concentration, adjusted for other predictors and obesity

	Incidence of hypertension (sBP of ≥ 165 mmHg or dBP of ≥ 95 mmHg)			Incidence of dyslipidemia (serum HDL cholesterol of <1.0 mmol/l or serum triglycerides of ≥ 2.3 mmol/l)			Incidence of the combination of hypertension and dyslipidemia		
	RR	95% CI	<i>P</i> value	RR	95% CI	<i>P</i> value	RR	95% CI	<i>P</i> value
Hyperinsulinemia at baseline	1.94	1.09–3.47	0.0253	2.12	1.32–3.41	0.0020	2.64	1.11–6.26	0.0283
Fasting serum insulin at baseline (mU/l)	1.06	1.01–1.11	0.0334	1.05	1.01–1.10	0.0208	1.04	0.96–1.14	0.3390

Hyperinsulinemia is defined as fasting serum insulin ≥ 12.0 mU/l (in the highest fifth of distribution). All models include the following covariates: age, the year of examination, time (h, min) of blood pressure measurements, history of hypertension in mother or father and, separately, in siblings, history of being overweight in mother, proportion of saturated of all serum fatty acids, mean blood pressure (mean of two sBP and two dBP values), serum triglycerides and HDL cholesterol, as well as BMI, WHR, and the change in weight during follow-up.

predicted incident hypertension in lean subjects, but the association disappeared after controlling for baseline blood pressure (17). Hyperinsulinemia was associated with the development of dyslipidemia independently of obesity and body fat distribution, while it predicted future hypertension in only lean normoglycemic subjects without a family history of diabetes in Mexican-Americans and non-Hispanic whites (14). Hyperinsulinemia also increased the incidence of lipid and lipoprotein abnormalities, including hypertriglyceridemia, in Finnish elderly nondiabetic people, but these relationships were largely explained by BMI and WHR (18). Together with these prospective studies (14–18), the independent associations of hyperinsulinemia with the incidence of hypertension and dyslipidemia in our study support the role of insulin resistance in the etiology of hypertension and dyslipidemia.

It has been speculated that the associations of hyperinsulinemia with hypertension and dyslipidemia are strongly confounded by obesity (9). Indeed, the relationship between hyperinsulinemia and hypertension has been largely explained by BMI in several cross-sectional studies (8,10) and was found only among lean subjects in two prospective studies (14,17). Furthermore, the associations of hyperinsulinemia with lipid and lipoprotein abnormalities were explained by BMI and WHR in one prospective study (18). In our study, however, the associations of hyperinsulinemia with the incidence of hypertension, dyslipidemia, and the combination of these disorders persisted after controlling for BMI, WHR, and the change in weight during the follow-up and was present both in lean and obese men. These findings strongly suggest that even though obesity is a major determinant of hyperinsulinemia, hypertension, and dyslipidemia, the impact of hyperinsulinemia on the risk of future hypertension and dyslipidemia is, for the most part, independent of obesity. In spite of this, weight reduction, either through restriction of energy intake or regular physical activity, remains the only effective way to prevent the occurrence of hyperinsulinemia and diabetes, as well as hypertension and dyslipidemia, both of which may be considered complications of insulin resistance.

A number of plausible pathophysiological mechanisms support causality of the associations observed in the present study. Insulin resistance has been proposed to 1) elevate serum triglycerides through increasing the production rate of VLDL and reducing the catabolism of VLDL due to low lipoprotein lipase activity and to 2) lower serum HDL cholesterol through decreasing the synthesis of HDL cholesterol from LDL triglycerides due to low lipoprotein lipase activity, elevating fractional catabolic rate of apolipoprotein A-1 (the major apolipoprotein for HDL cholesterol), elevating hepatic lipase concentration, and increasing cholesteryl ester transfer protein activity (2,10,12). Insulin resistance and/or subsequent hyperinsulinemia has been suggested to elevate blood pressure chronically by enhancing sympathetic nervous system activity, increasing renal tubular sodium reabsorption, modulating cation transport, inducing vascular smooth muscle cell hypertrophy (11), and by decreasing basal production of nitric oxide by the vascular endothelium (29). Experimental studies have shown that hyperinsulinemia per se does not acutely cause hypertension in spite of its effects on sympathetic nervous system and renal sodium reabsorption (11). Insulin itself has an acute vasodilating effect, which should lower rather than elevate blood pressure (9). However, the

vasodilating effect of insulin is blunted in obese hypertensive and insulin-resistant subjects (30–32). Sowers et al. (11) has suggested that prolonged hyperinsulinemia may contribute to the development of hypertension by promoting atherosclerosis and vascular remodeling. Indeed, insulin resistance has been observed to be associated with increased carotid wall thickness (33) and carotid artery plaques (34).

Certain antihypertensive drugs, such as high-dose thiazide diuretics and β -blockers, have been noted to exacerbate insulin resistance and dyslipidemia in hypertensive patients (35,36). In a synthesis of 474 clinical trials with 85 antihypertensive agents, nearly all antihypertensive agents were noted to affect serum lipids (37). β -blockers were observed to increase serum triglycerides, diuretics to increase serum cholesterol levels, and ACE inhibitors and α -blockers to lower triglycerides (37). In the present study, β -blockers but not diuretics were associated with an increased incidence of dyslipidemia. The lack of a significant effect of diuretics on serum triglycerides and HDL cholesterol could have been due to the relatively low doses used, but it is also consistent with previous studies. On the basis of previous and our data, ACE inhibitors and α -blockers, which may even improve insulin sensitivity (35,36), are preferable for the treatment of hypertension, especially in patients with metabolic abnormalities.

In conclusion, hyperinsulinemia was associated independently with an increased incidence of hypertension, dyslipidemia, and the combination of these disorders in an unselected population of men. This prospective population-based study supports the hypothesis implicating insulin resistance in the etiology of hypertension and dyslipidemia as well as the concept of the insulin resistance syndrome.

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