Hyperinsulinemia and Carotid Atherosclerosis in Hypertensive and Control Subjects

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OBJECTIVE — To analyze the relationships between carotid atherosclerosis measured as intima-media thickness (IMT) and different measures of insulin in a population-based case-control study of men and women.

RESEARCH DESIGN AND METHODS — Carotid ultrasonographic measurements and 2-h oral glucose tolerance tests were performed in a random sample of 513 hypertensive subjects, aged 40–59 years, and in 518 age- and sex-matched control subjects. The associations between IMT and the different measures of insulin were analyzed through multiple regression and by insulin quintiles. The independent effect of insulin was estimated after concurrent adjustment for age, obesity, LDL cholesterol, and systolic blood pressure.

RESULTS — The most powerful correlates with IMT were LDL cholesterol, age, systolic blood pressure, pack-years of smoking, and of the different insulin parameters, 2-h post-load insulin. In stepwise regression analysis, the independent predictors of the mean IMT were LDL cholesterol, systolic blood pressure, pack-years of smoking, and age ($P < 0.0001$) after adjustment for the independent predictors. In analysis of variance, no positive association of insulin parameters with IMT was found between the 2-h insulin quintiles after adjustment for the independent variables. The exclusion of diabetic subjects did not change the results.

CONCLUSIONS — The present study of a population-based sample of men and women found inconsistent associations between different insulin measures and IMT after adjustment for the independent variables.

Evidence suggests a direct role of insulin in the development of atherosclerosis through stimulation of vascular smooth muscle cell proliferation and arterial wall lipid deposition (1). Insulin has also been implicated as an indirect cause of atherogenesis through promoting the development of hypertension and dyslipidemia (2–5). High insulin levels have been shown to be an independent risk factor for ischemic heart disease in four prospective studies (6–9). Reaven (10) postulated that insulin resistance and compensatory hyperinsulinemia underlie the "syndrome X" (or the "insulin resistance syndrome"; later, the "cardiovascular metabolic syndrome"), which comprises the associations among insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia and hypertension, suggesting that this syndrome may be an important cause of atherosclerotic cardiovascular disease in affluent societies.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; BIF, bifurcation enlargement; CCA, common carotid artery; CPIMT, combined plaque–intima-media thickness; ICA, internal carotid artery; IMT, intima-media thickness; IRI, insulin resistance index; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; OPERA, Oulu Project Elucidating Risk of Atherosclerosis; QCS, Quebec Cardiovascular Study; WHO, World Health Organization; WHR, waist-to-hip ratio.

Carotid artery atherosclerosis measured with ultrasonography as intima-media thickness (IMT) has been associated with coronary artery disease (11–14). IMT has been used as a surrogate end point of the early atherosclerotic process (15), and it is reduced by lipid-lowering therapy (16,17).

The present study was designed to analyze the relationship between carotid atherosclerosis measured as IMT and different measures of insulin in a population-based case-control study of 1,031 men and women. The effect of insulin was estimated after concurrent adjustment for age, obesity, LDL cholesterol, and systolic blood pressure, increases in which have been repeatedly shown to be risk factors for atherosclerosis.

RESEARCH DESIGN AND METHODS

— Oulu Project Elucidating Risk of Atherosclerosis (OPERA) is a population-based, epidemiological case-control study addressing the risk factors and disease end points of atherosclerotic cardiovascular diseases. Out of the defined population of the city of Oulu (106,500 inhabitants), hypertensive men and women aged 40–59 years at the time of selection and receiving medication were recruited for the cardiovascular risk factor study (OPERA), along with age- and sex-matched control subjects from the Social Insurance Institution register. The hypertensive patients receiving medication (300 men and 300 women) were randomly selected by age stratification (15 subjects per year) from the Social Insurance Institution register for the reimbursement of the costs of antihypertensive medication. All analyses were performed according to the primary selection from the population registers. A detailed description of the subjects has been presented previously (18). All subjects volunteered to participate in the study, which was approved by the Ethical Committee of the University of Oulu.

The procedure for blood pressure measurement was in agreement with the recommendations of the American Society of Hypertension (19). All blood pressure measurements were recorded with an auto-

matic oscillometric blood pressure recorder (Dinamap; Critikon, Ascot, U.K.). The resting blood pressure was measured three times at 1-min intervals on the right arm after the patient had been seated for at least 5 min. The mean of the three sitting blood pressure measurements was used in the analysis. BMI was calculated as weight in kilograms divided by height in square meters. Details about the smoking habits, alcohol consumption, use of medications, and past medical history were sought in a questionnaire.

Carotid ultrasound method

A duplex ultrasound system was used according to the same protocol by a single trained radiologist blinded to the presence or absence of hypertension. A detailed description of the ultrasonographic assessment of carotid arteries has been presented previously (20). IMT and the size and number of atheromatous plaques were measured. IMT was measured at five locations on each side, on both the near and the far walls (20 sites in all): the internal carotid artery (ICA) ~1 cm distal from the flow divider, the bifurcation enlargement (BIF) and three locations of the common carotid artery (CCA), proximal, middle, and distal at ~1.0- to 1.5-cm intervals, depending on the length of the vessel. The examiner searched for the point of maximal IMT for measurement at each site, avoiding the sites of atheromatous plaques. In the case of a plaque, the combined plaque–intima-media thickness (CPIMT) was measured. If there was no plaque at the site of measurement, the IMT value alone was used for CPIMT.

The following measurements were used in the analyses: the overall mean (the mean of the CCA, BIF, and ICA near and far wall measurements), the overall far-wall mean, the overall and far-wall BIF mean, the overall and far-wall CCA mean, the overall and far-wall ICA and CPIMT mean, and the maximal IMT and CPIMT for each patient. The intra- and interobserver reproducibility of the measurement of IMT was assessed in 31 randomly selected subjects (10 men of age >57 years, 11 women <43 years, and 10 women >57 years). The measurements were performed from videotapes 1.5 years after examination of the subjects and without knowledge of the original result. The intrareader variability and the correlation coefficient for the mean IMT (CCA/BIF/ICA) were 3% and 0.97 (Pearson's coefficient), and for the maximal IMT, 9.9% and 0.94. Correspondingly, the interreader variability and correlation were 7.2% and 0.93 (mean mode) and 12.8% and 0.92 (maximal mode).

Laboratory analyses

A wide range of laboratory analyses were conducted. After the fasting blood had been drawn, the subjects were given a 75-g glucose load. Both 1- and 2-h glucose and insulin concentrations were determined. The glucose concentrations were measured with the glucose dehydrogenase method (Diagnostica; Merck, Darmstadt, Germany). Diabetes was defined according to the World Health Organization's (WHO) criteria, i.e., known diabetes or fasting blood glucose ≥6.7 mmol/l or 2-h blood glucose ≥10.0 mmol/l at the oral glucose tolerance test (OGTT), and impaired glucose tolerance was defined as fasting blood glucose <6.7 mmol/l but 2-h blood glucose 6.7–9.9 mmol/l.

The serum insulin levels were measured using a two-site immunoenzymometric assay (AIA-PACK IRI; Tosoh, Tokyo). The cross-reactivity of the assay was not measured. Several parameters of fasting insulin and insulinemic response in the OGTT—namely, the fasting, 1-h, and 2-h serum insulin concentrations; the insulin sensitivity index (ISI) (21); the insulin resistance index (IRI) (22); and the area under curve (trapezoidal method)—were calculated. Plasma lipids and lipoproteins were analyzed as described in the Lipid Research Clinics Program's *Manual of Laboratory Operations* (23).

Statistical analyses

The data were analyzed with the Statistical Analysis System (SAS, Cary, NC) on a VAX computer. The data are presented as means ± SD unless otherwise stated. The χ^2 test was used to test the differences in frequencies. The analysis of variance was used to compare more than two groups, and the adjustment for confounding factors was performed using the analysis of covariance in the general linear model or the regression model (24). Appropriate precautions in executing and interpreting the multivariable methods, including tests for interactions and for the stability of coefficients, were observed in accordance with a recent review (25). Bonferroni's correction was used in multiple tests. Student's two-tailed *t* test for independent samples was used in the comparisons of two groups. Because the near-wall measurements may be difficult to define (26), all analyses from near and far walls were performed separately. Subjects with missing data were excluded from the statistical analyses. In all the statistical analyses, logarithmic values for triglycerides and for all insulin values were used. *P* values <0.05 were considered statistically significant.

RESULTS — Table 1 shows the basic characteristics and cardiovascular risk factors of the hypertensive and control cohorts. The hypertensive subjects, both men and women, were significantly more obese and had a greater waist-to-hip ratio (WHR) than their age- and sex-matched controls. Systolic and diastolic blood pressures showed poor blood pressure control, especially in hypertensive men, of whom 70.1% had blood pressures exceeding 160/95 mmHg (WHO definition for hypertension). Both hypertensive cohorts had poorer metabolic control of glucose and insulin parameters than the control cohorts. The maximal IMT values, and mean and far-wall IMT and CPIMT values, have been presented previously (20). Men had significantly thicker mean IMT at all locations than women (0.86 mm [SD, 0.19] in the middle CCA, 0.98 mm [0.24] in BIF, and 0.84 mm [0.20] in ICA in men; 0.76 mm [0.10], 0.90 mm [0.16], and 0.73 mm [0.12] in women, respectively). There was a significant difference between the hypertensive and control men in the maximal CPIMT of the ICA/BIF/CCA (P = 0.007) and ICA (P = 0.002), and in the mean CPIMT of ICA (P = 0.005).

The correlation matrixes between the mean IMT and selected variables are presented in Tables 2 and 3. The most powerful correlates with IMT were LDL cholesterol, age, systolic blood pressure, and pack-years of smoking. LDL cholesterol correlated significantly more strongly with IMT in control men than in the other study groups. The correlation of pack-years of smoking with IMT was significantly stronger in men than in women. Only hypertensive women showed no significant correlation between pack-years of smoking and IMT. Several parameters of fasting insulin and insulinemic response in the OGTT—the fasting, serum 1-h, and 2-h insulin concentrations, ISI (21), IRI (22), and the area under curve (trapezoidal method)—were statistically tested with IMT. The most powerful and consistent predictor of IMT among the different insulin parameters in stepwise regression analyses was 2-h postload insulin, which

Table 1—*Basic characteristics and cardiovascular risk factors of hypertensive and control cohorts*

	Men		Women	
	Control	Hypertensive	Control	Hypertensive
n	253	258	265	255
Age (years)	51 ± 6	51 ± 6	52 ± 6	52 ± 6
Weight (kg)	82 ± 13	90 ± 15*	68 ± 12	74 ± 15*
BMI (kg/m^2)	26.5 ± 3.5	29.4 ± 4.4†	26.2 ± 4.5	28.7 ± 5.3†
WHR	0.91 ± 0.06	0.95 ± 0.06*	0.78 ± 0.06	0.82 ± 0.06*
Systolic blood pressure (mmHg)	147 ± 20	160 ± 20†	139 ± 21	154 ± 20†
Diastolic blood pressure (mmHg)	89 ± 11	98 ± 10 †	82 ± 12	91 ± 11†
Heart rate (beats/min)	72 ± 15	73 ± 15	75 ± 11	76 ± 13
Total cholesterol (mmol/l)	5.77 ± 1.09	5.76 ± 1.02	5.54 ± 1.03	5.72 ± 1.05
LDL cholesterol (mmol/l)	3.73 ± 0.97	3.59 ± 0.92	3.33 ± 0.92	3.47 ± 0.92
HDL cholesterol (mmol/l)	1.22 ± 0.30	1.18 ± 0.31	1.56 ± 0.38	1.44 ± 0.38†
Triglycerides (mmol/l)	1.38 (1.0, 1.84)	1.61 (1.21, 2.29)†	1.04 (0.83, 1.31)	1.34 (0.98, 1.92)*
Fasting blood glucose (mmol/l)	4.57 ± 1.06	5.13 ± 1.91†	4.34 ± 0.57	4.92 ± 1.82†
2-h glucose (mmol/l)	5.29 ± 2.36	6.61 ± 3.43†	5.43 ± 2.04	6.68 ± 3.59†
Fasting serum insulin (mU/l)	10 (7.9, 15)	15 (10, 21)	8 (6, 12)	11 (8, 17)
2-h insulin (mU/l)	40 (25, 64)	66 (37, 109)†	44 (30, 65)	59 (39, 103)†
ISI [(mg · l^2) /(mmol · mU · min)]	101 (81, 123)	77 (56, 100)†	103 (81, 128)	86 (59, 108)†
IRI (insulin resistance unit)	2.78 ± 2.97	4.38 ± 4.47†	1.92 ± 1.47	3.24 ± 3.35*
AUC_{INS} (mU/l · h)	98 (62, 163)	138 (87, 215)†	89 (63, 136)	117 (75, 187)†
Alcohol consumption (absolute g/week)	88 ± 98	105 ± 127	23 ± 36	30 ± 47
Impaired glucose tolerance/diabetes (%)	9.5/4.7	20.5†/16.7†	13.6/3.8	20.0/12.6†
Smokers (%)	39.1	28.3*	27.6	22.0

Data are *n*, means ± SD, or % except for triglycerides, fasting serum insulin, 2-h insulin, ISI, and AUC_{INS} (insulinemic area under the curve [trapezoidal method]), which are medians (25, 75 interquartile range). Values for ISI and IRI were calculated according to the methods of Cederholm and Wibell (21) and Matthews et al. (22), respectively. All statistical differences are $P < 0.05$. *Cohort versus control cohort. †Cohort versus control cohorts of both sexes.

was used in subsequent analyses alone without any other insulin parameters in order to prevent multicollinearity. In the control groups, 2-h insulin had a weak, nonsignificant positive correlation with IMT, but in the hypertensive groups, it had a weak nonsignificant negative correlation with IMT (Tables 2 and 3).

To determine whether an independent association between IMT and different insulinemic measures existed, multiple forward and backward stepwise regression analyses

Table 2—*Correlation matrix of IMT and selected variables in control and hypertensive men*

	IMT	Age	BMI	Blood pressure		Pack-years	LDL cholesterol	Fasting blood glucose	2-h glucose	Fasting serum insulin	2-h insulin	ISI	AUC_{INS}
				Systolic	Diastolic								
	Control men												
IMT		0.28*	0.09	0.20*	0.07	0.25*	0.37*	−0.02	−0.06	0.08	0.06	−0.0	0.08
Age	0.33*		0.04	0.14‡	0.02	0.18†	0.07	0.06	0.06	0.0	0.18†	−0.15‡	0.10
BMI	0.08	0.09		0.28*	0.29*	−0.02	0.04	0.21*	0.20*	0.47*	0.33*	−0.30*	0.45*
Systolic blood pressure	0.23*	0.21*	0.28*		0.78*	−0.01	0.02	0.29*	0.23*	0.24*	0.20*	−0.28*	0.18†
Diastolic blood pressure	0.03	0.04	0.20†	0.72*		−0.04	−0.0	0.24*	0.19†	0.18†	0.17†	−0.24*	0.19†
Pack-years	0.26*	0.08	0.08	0.11	0.0		0.17†	−0.01	−0.05	−0.0	−0.02	0.0	0.0
LDL cholesterol	0.16†	−0.03	0.01	−0.0	0.0	0.03		−0.13‡	−0.14‡	0.11	0.05	−0.01	0.11
Fasting blood glucose	0.08	0.15†	0.27*	0.17†	0.09	−0.0	−0.06		0.80*	0.20†	0.0	−0.42*	−0.05
2-h glucose	0.01	0.21*	0.23*	0.20†	0.09	−0.04	−0.08	0.83*		0.21*	0.28*	−0.68*	0.01
Fasting serum insulin	−0.05	−0.07	0.51*	0.11	0.16†	0.04	0.03	0.28*	0.22*		0.52*	−0.56*	0.58*
2-h insulin	−0.09	0.05	0.31*	0.0	0.03	−0.06	0.07	−0.09	0.18†	0.50*		−0.77*	0.70*
ISI	0.10	−0.14‡	−0.40*	−0.18†	−0.15‡	0.05	−0.03	−0.49*	−0.73*	−0.54*	−0.66*		−0.42*
AUC_{INS}	−0.04	−0.06	0.33*	−0.01	0.02	0.06	0.10	−0.19†	−0.09	0.56*	0.73*	−0.30*	
	Hypertensive men												

ISI was calculated according to the method of Cederholm and Wibell (21). *$P < 0.001$; †$P < 0.05$; ‡$P < 0.01$. AUC_{INS}, insulinemic area under the curve after glucose load; pack-years, pack-years of smoking.

Table 3—*Correlation matrix of IMT and selected variables in control and hypertensive women*

	IMT	Age	BMI	Blood pressure: Systolic	Blood pressure: Diastolic	Pack-years	LDL cholesterol	Fasting blood glucose	2-h glucose	Fasting serum insulin	2-h insulin	ISI	AUC_{INS}
						Control women							
IMT		0.34*	0.05	0.28*	0.12‡	0.13†	0.17‡	0.12†	0.02	0.08	0.05	-0.08	0.13†
Age	0.36*		0.22*	0.29*	0.18‡	0.04	0.32*	0.21*	0.26*	0.12	0.19‡	−0.25*	0.15†
BMI	−0.12	0.02		0.23*	0.27*	0.18‡	0.16‡	0.35*	0.30*	0.49*	0.29*	−0.40*	0.32*
Systolic blood pressure	0.20‡	0.17‡	0.17‡		0.77*	−0.01	0.09	0.27*	0.20*	0.19‡	0.25*	−0.30*	0.25*
Diastolic blood pressure	0.06	0.06	0.06	0.74*		−0.02	0.09	0.26*	0.18‡	0.15†	0.18‡	−0.24*	0.21*
Pack-years	0.06	0.02	−0.02	−0.07	−0.03		0.11	0.02	−0.10	0.20‡	−0.03	0.0	0.11
LDL cholesterol	0.13†	0.29*	0.14†	0.05	−0.0	−0.05		0.07	0.08	0.16‡	0.20‡	−0.18‡	0.12
Fasting blood glucose	−0.0	0.04	0.22*	0.04	−0.06	−0.01	0.02		0.66*	0.36*	0.19‡	−0.51*	0.11
2-h glucose	0.04	0.12	0.24*	0.14†	−0.0	−0.04	0.06	0.88*		0.27*	0.42*	−0.72*	0.17‡
Fasting serum insulin	−0.11	0.05	0.62*	0.03	−0.08	0.06	0.10	0.29*	0.26*		0.51*	−0.61*	0.54*
2-h insulin	−0.12	0.07	0.43*	0.17†	0.07	−0.02	0.09	0.08	0.25*	0.65*		−0.79*	0.69*
ISI	0.04	−0.10	−0.50*	−0.20*	−0.01	0.02	−0.10	−0.53*	−0.71*	−0.67*	−0.74*		−0.46*
AUC_{INS}	−0.12	0.05	0.42*	0.12	−0.01	0.05	0.08	0.04	0.08	0.68*	0.80*	−0.54*	
						Hypertensive women							

ISI was calculated according to the method of Cederholm and Wibell (21). *$P < 0.001$; †$P < 0.05$; ‡$P < 0.01$. AUC_{INS}, insulinemic area under the curve after glucose load; pack-years, pack-years of smoking.

(Table 4) were performed with different IMT parameters as the dependent variables, and age, pack-years of smoking, LDL cholesterol, systolic blood pressure, and 2-h insulin as the independent variables (data on serum 1-h and 2-h insulin concentrations, ISI, IRI, and insulinemic area under the curve not shown). The independent variables were selected on the basis of the predictive power and consistency in different groups. Age was the strongest independent predictor of IMT in all analyses, most consistently in the study groups (multiple correlation coefficient was between 0.07 and 0.13). LDL cholesterol was the strongest predictor of IMT in control men only. Serum 2-h insulin remained significant in hypertensive women only after adjustment for the effect of age (data not shown). The mean values of the various IMT measures did not differ significantly among the quintiles of 2-h insulin, but most showed a negative trend with increases in insulin (data not shown).

To improve the power to detect the possible significant relationship of ISI, IRI, insulin-to-glucose ratio, fasting insulin, 1-h insulin, 2-h insulin, or area under the curve to the mean IMT, a pooled analysis of 1,005 subjects was performed after adjusting for the effects of sex, age, systolic blood pressure, BMI, and LDL cholesterol. Stepwise regression analysis showed the independent predictors of the mean IMT to be LDL cholesterol, systolic blood pressure, pack-years of smoking, and age ($P < 0.0001$). The most powerful variable of insulin measures was 2-h insulin, which did not reach statistical significance ($P = 0.14$). The 2-h insulin explained only 0.2% of the variance of the mean IMT after adjustment for the independent predictors. The exclusion of diabetic subjects did not change the results. The indicator variables of case or control status and the presence or absence of diabetes were introduced in the regression models. In a pooled analysis, the effects of indicator variables and their interaction were not significant.

CONCLUSIONS — Most clinical studies have addressed the association of an increased insulin response to oral glucose in patients with atherosclerotic vascular disease (1). Four large prospective population studies (6–9) have shown the association between high insulin concentrations and an increased risk of cardiovascular disease in men; only one study has shown this association in women (27). However, all of these studies except the Quebec Cardiovascular Study (QCS) (9) and the Atherosclerosis Risk in Communities (ARIC) Study (32) lacked the measurement of the potentially confounding variable, HDL cholesterol. Also, the QCS used a radioimmunoassay that did not cross-react with proinsulin and that had not been used in the previous studies. Seven recent prospective studies revealed no association between high insulin

Table 4—*Multiple stepwise regression analyses of the mean IMT with risk factors in control and hypertensive men and women*

	Men		Women	
	Control	Hypertensive	Control	Hypertensive
n	259	261	267	258
Age	0.06*	0.09*	0.07*	0.10*
Pack-years of smoking	0.02*	0.05*	0.02*	<0.01
LDL cholesterol	0.13*	<0.03	0.03*	0.03*
Systolic blood pressure	0.03*	0.04*	0.06*	0.07*
2-h insulin	<0.01	0.01	<0.01	<0.01
Model R^2 (%)	24	22	18	20

Data are multiple correlation coefficients (R^2), which represent the percentage of variance explained by the independent variable (risk factor) after adjusting for age, BMI, LDL cholesterol, and systolic blood pressure. *$P < 0.05$.

levels and increased coronary heart disease risk, as pointed out in a recent review (28). Two prospective studies (29,30) even demonstrated an inverse association between postchallenge insulin levels and cardiovascular disease in men.

In the present study, IMT was independently associated with the established risk factors for atherosclerosis: smoking and increased age, LDL cholesterol, and systolic blood pressure. These results are consistent with some earlier studies (11,12,31). We did not find any significant associations between BMI, WHR, physical activity, and IMT, which is contradictory to the ARIC Study (32) but agrees with Salonen and Salonen (31). The independent predictors of IMT explained only 18% of the variance in IMT, which is in accordance with some earlier reports (18,31). The possible reasons that have been given for this small amount of variance are the possible weaker associations with carotid atherosclerosis than with coronary atherosclerosis, measurement error of IMT, genetic susceptibility, hemostatic factors, imprecise measurement of risk factors, and unknown confounding biases (32).

In the ARIC Study (32), after adjustment of fasting serum insulin for the established cardiovascular risk factors, the effect of insulin was reduced to a nonsignificant level in women ($P = 0.06$) and to borderline significance in men ($P = 0.04$). The main result of the present study remains essentially unchanged, although the insulin values were adjusted for age, pack-years of smoking, BMI, hypertension, and LDL and HDL cholesterol, as in the ARIC Study. The failure to find a consistent association between insulin and atherosclerotic vascular disease suggests that the relationship may be weak and, thus far, significant only in middle-aged Caucasian men and women (27,33). Some observed differences between the hypertensive and control subjects in the present study may partly be explained by the effects of certain types of antihypertensive medication on the relationship between insulin and IMT. Hypertensive patients, who receive medical care by physicians, may be more likely to receive other therapy, including cholesterol-lowering medication.

The present study of a population-based sample of men and women found inconsistent associations between different insulin measures and IMT after adjustment for the independent variables. The effect of insulin on atherosclerosis is also less powerful than that of the established cardiovascular risk factors, such as smoking and increased age and LDL cholesterol.

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