DM

Relation between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects. Results from a cross-sectional study in Malmö, Sweden

B. Hedblad*†, P. Nilsson*, L. Janzon† and G. Berglund*

*Department of Medicine and †Department of Community Medicine, Lund University, Malmö University Hospital, Malmö, Sweden

Received 14 September 1999; revised 26 January 2000; accepted 6 February 2000

Abstract

Aims To assess whether there is an association between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects free from symptomatic cardiovascular disease.

Methods A cross-sectional population-based study in Malmö, Sweden, of 4816 (40% men) subjects, born 1926–1945. The prevalence of insulin resistance was established by the homeostasis model assessment (HOMA) and defined as values above the 75th percentile. Criteria issued by the European Group for the Study of Insulin Resistance (EGIR) were used for the definition of the insulin resistance syndrome. Common carotid artery intima-media thickness (IMT) and carotid stenosis (> 15%) were measured by B-mode ultrasonography.

Results Age and sex-adjusted common carotid IMT among subjects with the insulin resistance syndrome (12.7%) and controls was 0.812 mm, respectively, 0.778 mm ($P < 0.001$). The prevalence of stenosis in the two groups was 22.9 and 19.2% ($P = 0.040$). Insulin resistance *per se* was after adjustment for age and sex associated with increased IMT (0.780 mm vs. 0.754 mm, $P < 0.001$). This association disappeared, however, when other factors included in the insulin resistance syndrome were taken into account.

Conclusions Fasting serum insulin covaries with a number of factors and conditions known to influence the development of atherosclerosis. It is concluded that the association between insulin resistance, as assessed by the HOMA method in non-diabetic subjects, and atherosclerosis is explained by its covariance with established risk factors for cardiovascular disease of which hypertension seems to be the most significant.

Diabet. Med. 17, 299–307 (2000)

Keywords atherosclerosis, carotid ultrasound, HOMA, insulin resistance

Abbreviations BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IMT, intima-media thickness; LDL, low-density lipoprotein

Introduction

The issue of whether insulin resistance may enhance the development of atherosclerosis remains controversial [1–5]. Differences between studies [6–11] with regard to

Correspondence to: Dr Bo Hedblad, Department of Community Medicine, Lund University, Malmö University Hospital, S-205 02 Malmö, Sweden.

eligibility criteria, i.e. whether patients with diabetes mellitus and symptomatic atherosclerosis have been excluded or not, as well as differences with regard to the definition of insulin resistance and control in the statistical analysis for its known covariance with hyperglycaemia, hypertension, dyslipidaemia and central obesity, e.g. factors associated with the metabolic syndrome [5,12] or insulin resistance syndrome [13], are some of the possible contributors to the lack of consistency.

By using the B-mode ultrasound technique it is now possible to assess whether insulin resistance has any relationship to a very early stage in the development of artherosclerosis, i.e. an increase of the intima-media complex of the carotid or femoral wall [14–18].

The objective in this cross-sectional population-based study has been to compare intima-media thickness (IMT), and the prevalence of stenosis in the carotid artery in groups defined in terms of insulin resistance, as assessed by the homeostasis model assessment (HOMA) [19], and other conditions included in the insulin resistance syndrome [13].

Subjects and methods

The 4816 study subjects, 1915 men and 2901 women, born between 1926 and 1945, belong to the Malmö 'Diet and Cancer' study cohort [20]. A random 50% of those who entered the study between November 1991 and February 1994 were invited to take part in a study on the epidemiology of carotid artery disease. The 5540 who accepted were re-scheduled for blood sampling under standardized circumstances on average 8 months later.

The 238 subjects who had diabetes mellitus (i.e. history of diabetes or fasting blood glucose exceeding 6.7 mmol/l [21]), and the 242 who according to the self-administered questionnaire had cardiovascular disease (i.e. myocardial infarction, stroke or peripheral arterial disease) were not eligible for the present study. Another 244 individuals were excluded because of incomplete data.

The study was approved by the Ethics Committee at Lund University. Each proband gave his or her informed consent.

Clinical data

A self-administered structured questionnaire was used for the assessment of smoking habits, physical activity, alcohol consumption and use of medication. Smoking habits were categorized into never-smokers, former smokers and current smokers.

Seventeen structured activities together with open alternatives were used to describe physical activity during leisure time. For each of these activities participants were asked how many minutes they on average spent per week during each season. Average time was multiplied by an intensity factor, which ranged from 4 to 8, to create an activity index [22]. Five categories (quintiles) were used in the analysis, i.e. low (Q1), moderate (Q2–Q4), and high (Q5).

Average daily alcohol consumption (in g) is based on the subjects' own recording of foods and beverages consumed during seven consecutive days [23].

Physical examination data

Blood pressure (mmHg) was measured once after 10 min rest while the subject was in a supine position. Probands who had a systolic blood pressure of 160 mmHg or more, a diastolic blood pressure of 95 mmHg or more, or who used blood pressure lowering medication, were classified as having hypertension.

Weight (kg) and height (m) were measured while the probands wore light indoor clothing and were without shoes. Body mass index (BMI) was calculated as kg/m^2 as a measure of overall obesity. Obesity was defined as BMI $\geq$ 30 $kg/m^{2.}$ Waist circumference was measured at the umbilicus. The cut-off value for definition of central obesity was for men 94 cm and for women 80 cm [24].

Laboratory analyses

After overnight fasting blood samples were drawn for the determination of serum values of total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, insulin and whole blood glucose. Analyses were carried out at the Department of Clinical Chemistry, Malmö University Hospital, which is attached to a recurrent standardization system. Insulin levels were measured in mIU/l by radioimmunoassay [25]. The lower limit of detection for insulin was 3 mIU/l. Intra-assay and interassay coefficients of variation were 5 and 8%. LDL-cholesterol in mmol/l was calculated from the values for triglycerides, total cholesterol and HDL-cholesterol according to the Friedewald formula: LDL = total cholesterol – HDL – (triglycerides/2.2) [26].

HDL-cholesterol values below 0.9 (for women below 1.0) and triglycerides above 2.3 mmol/l alone or in combination were used as criteria for dyslipidaemia.

Definition of insulin resistance and the insulin resistance syndrome

Fasting insulin $\times$ fasting glucose/22.5 were in accordance with the HOMA model calculated for each individual [19]. Subjects whose values exceeded the 75th percentile (i.e. 2.0) were considered to have insulin resistance (HOMA IR) [13].

The insulin resistance syndrome was defined in accordance with the recently published criteria proposed by EGIR (the European Group for the Study of Insulin Resistance), i.e. by presence of insulin resistance or fasting hyperinsulinaemia in combination with at least two of the following conditions, hyperglycaemia, hypertension, dyslipidaemia or central obesity [13].

B-mode ultrasound vasculography

An Acuson 128 Computed Sonography System (Acuson, Mountain View, CA) with a 7-MHz transducer was used for the assessment of IMT in the right carotid artery. The

examination procedure and the image analysis which has been described previously [27,28] was performed by specially trained sonographers certified upon completion of an extensive programme [29]. In short, the carotid bifurcation is scanned within a predefined window comprising 3 cm of the of the distal common carotid artery, the bulb and 1 cm of the internal and external carotid artery, respectively, for the presence of plaques, defined as focal thickenings of the arterial wall. IMT was determined in the far wall of the distal common carotid artery according to the leading edge principle, using a specially designed computer-assisted image analysing system. The extent of early atherosclerotic lesions is thus determined off-line as the mean far wall thickness 1 cm proximal to the bifurcation, and late atherosclerotic lesions are defined on-line according to the presence of one or more plaques. Each image was analysed without knowledge of the subject's identification code to minimize the possibility of observer bias.

When a plaque was present, the degree of stenosis was assessed by measuring blood flow velocity at the location of maximum lumen diameter reduction. When no increase in flow velocity (change in Doppler shift) was detected at the site of plaque, the degree of stenosis was judged by 'eye-balling' the degree of plaque protrusion (maximum 30%) [28]. A lumen reduction of more than 15% was required to be counted as stenosis [30]. Assessment of stenosis had in 618 cases to be omitted as a result of technical problems. Subjects with missing values for carotid stenosis were somewhat older (58.2 years vs. 57.3 years), had higher common carotid IMT (0.775 vs. 0.758 mm) and higher fasting insulin (8.1 vs. 7.4 mIU/l).

Intra-observer and interobserver variability with regard to IMT was checked regularly. The mean intraobserver difference was $8.7 \pm 6.2\%$ ($r = 0.85$) and the mean interobserver difference $9.0 \pm 7.2\%$ ($r = 0.77$) [28].

Statistical analyses

SPSS (Chicago, IL) was used for the statistical analysis. Fasting insulin, HOMA, triglycerides and alcohol consumption values were log transformed to improve normality. For each sex, Pearson's correlation coefficient was used to estimate associations between common carotid IMT and age, blood pressure, obesity parameters and metabolic components. As there were large differences in the distribution of common carotid IMT in men and women [28] sex-specific distributions of IMT were used for cut-off points of quartiles. Age-adjusted mean values of the baseline characteristics and test of trend were calculated across these quartiles for continuous variables by including quartiles of common carotid IMT as ordinal variables in a linear regression models, and by Cochran–Mantell–Haenzel's test of association for dichotomous variables.

Linear regression was used to estimate the relationship between HOMA and common carotid IMT. In the first model adjustment was made only for age. In the extended model further adjustment was made for alcohol consumption, HDL-cholesterol, LDL-cholesterol, systolic blood pressure and waist circumference as continuous variables, and smoking habits, use of lipid or blood-pressure lowering medication as dichotomous variables. Physical activity and triglycerides were omitted in the

Table 1 Carotid intima-media thickness (IMT) and carotid stenosis in relation to exposure to different components (insulin resistance, hypertension, dyslipidaemia and central obesity) in the insulin resistance syndrome in non-diabetic subjects. Figures have been adjusted for age and sex

Group	IR	HT	DL	CO	*n*	IMT (mm)	Stenosis (%)
1	No	No	No	No	1897	0.741	17.1
2	No	No	No	Yes	456	0.744	15.1
3	No	No	Yes	No	119	0.752	28.8
4	No	No	Yes	Yes	70	0.732	10.4
5	No	Yes	No	No	658	0.772	25.8
6	No	Yes	No	Yes	314	0.795	21.1
7	No	Yes	Yes	No	56	0.794	22.9
8	No	Yes	Yes	Yes	59	0.794	21.9
9	Yes	No	No	No	184	0.745	23.6
10	Yes	No	No	Yes	260	0.770	15.2
11	Yes	No	Yes	No	36	0.804	18.2
12*	Yes	No	Yes	Yes	110	0.752	20.4
13	Yes	Yes	No	No	95	0.792	17.1
14*	Yes	Yes	No	Yes	299	0.798	23.2
15*	Yes	Yes	Yes	No	44	0.798	24.5
16*	Yes	Yes	Yes	Yes	159	0.806	24.2

IR, insulin resistance: according to the homeostasis model assessment (HOMA), i.e. upper quartile of the HOMA distribution.
HT, hypertension: systolic blood pressure ⩾ 160 mmHg or diastolic blood pressure ⩾ 95 mmHg or blood pressure lowering treatment.
DL, dyslipidaemia: serum triglycerides ⩾ 2.3 mmol/l or high-density lipoprotein (HDL)-cholesterol < 1.0 mmol/l for women and < 0.90 mmol/l for men.
CO, central obesity: waist circumference ⩾ 0.80 cm for women or ⩾ 94 cm for men.
IMT, common carotid intima-media thickness; Stenosis; moderate to severe carotid artery stenosis > 15%.
*Subjects defined as having the insulin resistance syndrome according to the European Group for the Study of Insulin Resistance (EGIR) definition [13].

Table 2 Correlation matrix (Pearson's correlation coefficients) of common carotid IMT and selected risk variables in non-diabetic men and women

Variable	Men (n = 1915)/women* (n = 2901)											
	IMT	Age	Fasting blood glucose	Log fasting insulin	Log HOMA	BMI	Waist circumference	HDL-cholesterol	Log triglycerides	Systolic blood pressure	Diastolic blood pressure
IMT	–	0.343†	0.113†	0.090†	0.101†	0.096†	0.102‡	–0.064‡	0.110†	0.308†	0.156†
Age	0.303†	–	0.121†	0.124†	0.135†	0.126†	0.118†	0.002	0.188†	0.357†	0.161†
Fasting blood glucose	0.122†	0.072‡	–	0.420†	0.555†	0.297†	0.322†	–0.154†	0.308†	0.210†	0.186†
Log fasting insulin	0.093†	0.066‡	0.371†	–	0.988†	0.478†	0.521†	–0.272†	0.404†	0.169†	0.165†
Log HOMA	0.106†	0.074‡	0.508†	0.988†	–	0.489†	0.532†	–0.276†	0.423†	0.191†	0.183†
BMI	0.105†	0.037	0.285†	0.498†	0.509†	–	0.857†	–0.283†	0.307†	0.221†	0.207†
Waist circumference	0.129†	0.083†	0.291†	0.515†	0.526†	0.873†	–	–0.342†	0.377†	0.215†	0.214†
HDL-cholesterol	–0.086†	0.020	–0.121†	–0.324†	–0.321†	–0.281†	–0.293†	–	–0.492†	– 0.068†	– 0.073†
Log triglycerides	0.035	0.012	0.235†	0.420†	0.428†	0.304†	0.316†	–0.510†	–	0.179†	0.183†
Systolic blood pressure	0.264†	0.284†	0.180†	0.159†	0.177†	0.205†	0.216†	–0.033	0.130†	–	0.726†
Diastolic blood pressure	0.132†	0.083†	0.157†	0.210†	0.221†	0.285†	0.284†	–0.069‡	0.150†	0.718†	–

IMT, intima-media thickness; HOMA, homeostasis model assessment; BMI, body mass index; HDL, high-density lipoprotein.
*Correlations for women are shown in the upper right corner of the matrix and for men in the lower left corner. †P < 0.001; ‡P < 0.01.

model as a result of their covariance with glucose and insulin metabolism and HDL-cholesterol. The model included waist circumference although there is causal relationship with glucose and insulin metabolism [31].

According to Rothman's 'pie' model of causation [32], exploring interaction and independence of effects, the cohort was also stratified for the presence or absence of insulin resistance, and further for the presence or absence of other metabolic components, i.e. hypertension, central obesity and dyslipidemia, respectively. Common carotid IMT and prevalence of stenosis have been calculated after adjustment for age and sex.

Results

IMT in relation to the insulin resistance syndrome

Six hundred and twelve (12.7%) subjects fulfilled the minimal criteria for the insulin resistance syndrome (i.e. groups 12, 14, 15 and 16), Table 1. One hundred and fifty-nine subjects, 3.3% (88 men and 71 women) were exposed to all factors/conditions required for the syndrome. The prevalence increased significantly with age and was more common in men than in women, 16.3 vs. 10.3%, corresponding to an age adjusted odds ratio of 1.7 (95% confidence interval (CI) 1.4–2.0). IMT was among those with the syndrome 0.812 mm and in the age and sex-adjusted control group 0.778 mm (P < 0.001). The prevalence of stenosis in the two groups was 22.9%, respectively, 19.2%, P = 0.040 (29.9% vs. 22.8% in men, P = 0.012, and 17.6% vs. 17.0% in women, P = 0.773).

Covariance between factors included in the insulin resistance syndrome

There was a strong covariance between the different parameters constituting the insulin resistance syndrome (Table 2).

Relationship of these factors with carotid IMT and stenosis

The prevalence and mean values of the conditions and factors included in the insulin resistance syndrome increased in a stepwise manner with increasing IMT (Tables 3 and 4). This pattern was stronger in men than in women. No similar association was found with regard to alcohol consumption or physical activity. The proportion of never-smokers covaried in a similar fashion with IMT.

The presence of stenosis was correlated with common carotid IMT, r = 0.31 and r = 0.30, for men and women, respectively (P < 0.001). This association remained after adjustment for age. Other factors associated with the prevalence of stenosis were blood pressure, current

Table 3 Age-adjusted baseline characteristics in relation to quartiles of common carotid intima-media thickness (IMT) in non-diabetic men

	Quartiles of IMT				
	1	2	3	4	*P*-value, trend
Number	504	471	487	453	
IMT (range, mm)	0.36–0.67	0.68–0.76	0.77–0.87	0.88–1.67	
Age (years)	55.0 ± 5.7	56.6 ± 5.9	58.4 ± 5.8	59.8 ± 5.6	
BMI (kg/m^2)	25.12	25.48	25.81	26.08	< 0.001
Obesity (BMI ⩾ 30) (%)	7.7	8.5	11.8	12.7	0.005
Waist (cm)	91.2	92.0	92.9	94.1	< 0.001
Central obesity (⩾ 94) (%)	34.5	39.4	41.5	50.2	< 0.001
Diastolic blood pressure (mmHg)	87.3	88.5	88.9	89.9	< 0.001
Systolic blood pressure (mmHg)	139.0	140.6	144.9	146.8	< 0.001
Hypertension (%)	30.0	35.4	43.0	46.1	< 0.001
BP lowering medication (%)	34.0	36.1	33.0	40.3	< 0.001
Blood glucose (mmol/l)	5.00	5.06	5.07	5.15	< 0.001
Fasting insulin (mIU/l)	7.71	7.69	8.13	9.46	0.001
HOMA	0.37	0.40	0.43	0.53	< 0.001
HOMA insulin resistance (%)	26.6	27.9	33.9	35.7	< 0.001
Total cholesterol (mmol/l)	5.93	5.93	6.05	6.14	< 0.001
Hypercholesterolaemia (⩾ 6.5) (%)	28.1	27.0	31.4	33.8	0.033
LDL (mmol/l)	4.05	4.03	4.16	4.30	< 0.001
LDL/HDL ratio (mmol/l)	3.53	3.52	3.69	3.89	< 0.001
HDL (mmol/l)	1.24	1.24	1.21	1.18	0.002
Low HDL (< 0.90) (%)	12.1	9.5	12.3	12.4	0.625
Triglycerides (mmol/l)	1.46	1.44	1.47	1.44	0.461
Hypertriglyceridaemia (⩾ 2.3) (%)	12.8	12.4	13.4	11.2	0.594
Dyslipidaemia† (%)	20.1	16.3	20.4	19.6	0.770
Lipid lowering medication (%)	0.8	2.0	3.3	2.5	0.016
Alcohol consumption (g/day)	14.9	16.9	14.8	14.8	0.693
Never smoked (%)	36.4	32.7	29.4	25.6	< 0.001
Former smokers (%)	38.3	37.6	43.4	44.8	0.019
Current smokers (%)	25.3	29.7	27.2	29.6	0.277
Low physical activity (%)	18.6	18.4	19.5	21.9	0.228
Carotid stenosis, > 15% (%)	13.8	21.2	26.4	36.7	0.009

IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HOMA, homeostasis model assessment; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
†Dyslipidaemia is defined as a low HDL-cholesterol < 0.90 mmol/l or hypertriglyceridemia ⩾ 2.3 mmol/l.

smoking, LDL-cholesterol, HDL-cholesterol (inverse in men), waist circumference (men), glucose (men) and triglycerides (men). No relationship was however, found with fasting insulin, HOMA or HOMA IR.

Multivariate analysis of the relationship between insulin resistance syndrome and IMT

Five hundred and ninety-five men and 592 women had insulin resistance (Table 1). In both men and women there was a statistically significant association between HOMA and common carotid IMT which remained statistically significant after adjustment for age (Table 5). The age and sex-adjusted IMT among those with insulin resistance was 0.780 mm and in the control group 0.754 mm ($P < 0.001$). Prevalence of carotid stenosis in the two groups was 20.6% and 19.3%, $P = 0.336$.

In the extended model, e.g. after adjustment for other factors included in the insulin resistance syndrome, there was no longer any significant association between insulin resistance and IMT. Exposure to hypertension was independent of insulin resistance associated with an increased IMT (Table 1).

Discussion

The higher prevalence of carotid stenosis and the increased carotid wall thickness in subjects with the insulin resistance syndrome is in line with findings in other studies of the occurrence of these abnormalities in relation to components involved in the syndrome [6–9,15,30,33,34]. However, there was no association between the syndrome and carotid stenosis among women. The reason for this is not clear but the relatively lower prevalence of atherosclerotic disease in women may lead to a reduced statistical power. Cardiovascular events occur around 10 years later in life in women than in men, which might explain the different odds ratios for men and women [35].

Table 4 Age-adjusted baseline characteristics in relation to quartiles of common carotid intima-media thickness (IMT) in non-diabetic women

	Quartiles of IMT				
	1	2	3	4	*P*-value, trend
Number	793	711	727	670	
IMT (range, mm)	0.36–0.66	0.67–0.73	0.74–0.82	0.83–1.58	
Age (years)	54.6 ± 5.6	56.6 ± 5.6	58.6 ± 5.6	60.1 ± 5.3	
BMI (kg/m2)	25.07	24.96	25.13	25.60	0.015
Obesity (BMI ⩾ 30) (%)	10.8	10.8	11.9	13.5	0.102
Waist (cm)	76.4	76.1	76.3	78.0	0.007
Central obesity (⩾ 80) (%)	31.5	30.5	30.3	36.8	0.068
Diastolic blood pressure (mmHg)	84.3	85.4	85.7	86.7	< 0.001
Systolic blood pressure (mmHg)	134.7	139.2	139.7	144.9	< 0.001
Hypertension (%)	25.8	29.8	32.1	40.2	< 0.001
BP lowering medication (%)	49.7	39.3	44.8	41.3	0.301
Blood glucose (mmol/l)	4.82	4.80	4.83	4.90	0.007
Fasting insulin (mIU/l)	7.00	6.97	7.14	7.39	0.169
HOMA	0.25	0.22	0.24	0.31	0.087
HOMA insulin resistance (%)	19.7	17.9	18.6	24.8	0.029
Total cholesterol (mmol/l)	6.23	6.17	6.25	6.44	< 0.001
Hypercholesterolaemia (⩾ 6.5) (%)	36.9	36.6	40.5	44.7	0.002
LDL (mmol/l)	4.14	4.10	4.18	4.40	< 0.001
LDL/HDL ratio (mmol/l)	2.91	2.83	2.94	3.18	< 0.001
HDL (mmol/l)	1.52	1.53	1.51	1.47	0.011
Low HDL (< 1.0) (%)	4.7	4.3	5.3	7.5	0.023
Triglycerides (mmol/l)	1.22	1.18	1.22	1.28	0.135
Hypertriglyceridaemia (⩾ 2.3) (%)	5.6	5.4	6.2	8.1	0.047
Dyslipidaemia† (%)	8.8	8.8	9.5	12.7	0.022
Lipid lowering medication (%)	2.8	2.2	0.8	3.4	0.914
Alcohol consumption (g/day)	7.1	7.2	6.6	7.0	0.542
Never smoked (%)	47.7	44.7	50.0	43.1	0.356
Former smokers (%)	27.3	27.9	25.1	27.8	0.838
Current smokers (%)	24.4	26.8	24.3	28.6	0.208
Low physical activity (%)	18.8	20.3	20.3	21.3	0.312
Carotid stenosis, > 15% (%)	13.0	13.8	15.8	28.1	< 0.001

IMT, intima-media thickness; BMI, body mass index; BP, blood pressure; HOMA, homeostasis model assessment; HDL, high-density lipoprotein; LDL, low-density lipoprotein. † Dyslipidaemia is defined as a low HDL-cholesterol < 1.0 mmol/l or hypertriglyceridemia ⩾ 2.3 mmol/l.

Subjects who fulfil the minimum criteria for the syndrome constitute, with regard to the combination of risk factors, a rather heterogeneous group. Although the prevalence of the syndrome was 12.7%, only 3.3% fulfilled all the criteria. In the British Regional Heart Study [36] in middle-aged men, free from cardiovascular disease and diabetes mellitus, the prevalence of the full metabolic syndrome (i.e. hypertension, hyperglycaemia and dyslipidaemia) was only 2.9%. However, when obesity and hyperinsulinaemia were added as criteria, the prevalence increased to 16%, i.e. close to the present figure (16.3%) for men. Differences in prevalence within Sweden [37,38] or elsewhere may have been confounded by selection bias as a result of non-response. Analysis of non-participants in the Malmö 'Diet and Cancer' study [20] have shown an overrepresentation of non-Swedish, younger men and the mortality rate so far in the cohort is only one-third of the expected (unpublished data).

The insulin resistance syndrome was initially described with insulin resistance being the central component [39]. Fasting insulin concentrations and HOMA were in the present study correlated with a number of cardiovascular risk factors, and the magnitude of the correlations was similar those reported by others [40]. Hence it may be difficult to completely adjust for this covariance in the evaluation of the relationship between HOMA IR and carotid atherosclerosis. It has been shown in one study, including only hypertensive men without history of diabetes mellitus or symptomatic cardiovascular disease, using the euglycaemic clamp technique, that the influence of insulin resistance on common carotid IMT was independent of body mass index [8].

The current study does not support the view that insulin alone has an influence on the development of atherosclerosis [1]. The absence of an independent influence of insulin resistance on common carotid IMT may indicate that no such relationship exists. An alternative explanation is that the relationship may have been confounded by invalid assessment of IMT, insulin and other risk factors associated with atherosclerosis.

Table 5 Adjusted regression coefficients (β) for multiple linear regressions of common carotid intima-media thickness (mm) on cardiovascular risk factors in non-diabetic subjects free of symptomatic cardiovascular disease

	Age-adjusted model		Extended model*	
Characteristic	β	P	β	P
Men				
Age (years)	0.0103	< 0.001	0.0087	< 0.001
Log HOMA (1 unit)	0.0267	< 0.001	0.0021	0.803
Former smoking (yes vs. no)			0.0302	0.003
Current smoking (yes vs. no)			0.0337	0.003
Log alcohol consumption (1 g)			– 0.0001	0.985
LDL-cholesterol (mmol/l)			0.0202	< 0.001
HDL-cholesterol (mmol/l)			– 0.0335	0.029
Lipid lowering medication (yes vs. no)			0.0607	0.061
Systolic blood pressure (mmHg)			0.0017	< 0.001
Hypertension medication (yes vs. no)			0.0280	0.028
Waist circumference (cm)			0.0009	0.103
Model R^2	0.107		0.159	
Women				
Age (years)	0.0101	< 0.001	0.0077	< 0.001
Log HOMA (1 unit)	0.0135	0.009	– 0.0006	0.919
Former smoking (yes vs. no)			0.0063	0.531
Current smoking (yes vs. no)			0.0155	0.034
Log alcohol consumption (1 g)			0.0016	0.659
LDL-cholesterol (mmol/l)			0.0133	< 0.001
HDL-cholesterol (mmol/l)			– 0.0166	0.058
Lipid lowering medication (yes vs. no)			0.0157	0.531
Systolic blood pressure (mmHg)			0.0019	< 0.001
Hypertension medication (yes vs. no)			0.0060	0.494
Waist circumference (cm)			– 0.0001	0.792
Model R^2	0.127		0.173	

IMT, intima-media thickness; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*The coefficients in the model are adjusted for the characteristics named under the model.

A pertinent issue is whether the HOMA model [19] is a valid method for the assessment of insulin resistance. The correlation with the hyperinsulinaemic-euglycaemic clamp technique has, in studies on non-diabetic subjects, been found to be 0.7 [41]. Furthermore, it has been demonstrated that insulin resistance as assessed by the HOMA score is a predictor of the development of non-insulin dependent Type 2 diabetes mellitus [42]. It has therefore been proposed that in population-based studies, where the euglycaemic-clamp technique is not feasible, HOMA is a useful method to assess insulin resistance [43,44].

Yet another relevant issue is whether the measurements of IMT can be used as a valid method to assess an individual's degree of early atherosclerosis. In the present study there was a significant relationship between common carotid IMT and the prevalence of stenosis. It has been demonstrated that the incidence of coronary heart disease covaries with the degree of IMT [45], and that a thick intima-media can predict cardiovascular events [17,46,47]. However, in a cross-sectional study it is not possible to assess whether a high value reflects progression as a result of exposure to known risk factors. Possible explanations for the small amount of variance in IMT found in this as in other studies [7,10] has been discussed previously [7].

Post-prandial plasma glucose has recently been identified in non-diabetic individuals as an independent risk factor for increased carotid IMT [48]. Results in published studies on the relationship between insulin resistance and early atherosclerosis are equivocal [6–11]. Although in the Insulin Resistance Atherosclerosis Study (IRAS) there was an independent relationship between insulin sensitivity and carotid atherosclerosis, there was no similar association with fasting insulin or 2-h insulin levels and the common or internal carotid IMT [9]. The association between fasting insulin and carotid IMT in the Atherosclerosis Risk in Communities (ARIC) study was, after adjustment for cardiovascular risk factors, only of borderline significance in men [7]. Two recently published studies [10,11] failed to show an independent association between fasting insulin and carotid IMT in hypertensive, respectively, non-diabetic subjects. The weak correlation (r = 0.10) between fasting insulin and common carotid IMT in the present study was in accordance with others

[10]. Whether this correlation would be improved by several measurements on each subject remains to be evaluated.

Fasting serum insulin covaries with a number of factors and conditions known to influence the development of atherosclerosis. It appears that the association between insulin resistance, as assessed by the HOMA method in non-diabetic subjects, and atherosclerosis is explained by its covariance with established risk factors for cardiovascular disease of which hypertension seems to be the most significant.

Acknowledgements

The study was supported by grants from the Swedish Cancer Society, the Medical Research Council, the Swedish Heart and Lung Foundation, the King Gustav V Jubilee Foundation, and by the Ernhold Lundström Foundation.

References

1 Stout RW. The impact of insulin upon atherosclerosis. *Horm Metabol Res* 1994; **26:** 125–128.
2 DeFronzo RA, Ferraninni E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; **14:** 173–194.
3 Wingard DL, Barett-Connor EL, Ferrara A. Is insulin really a heart disease risk factor? *Diabetes Care* 1995; **18:** 1299–1304.
4 McKeigue P, Davey G. Associations between insulin levels and cardiovascular disease are confounded by comorbidity. *Diabetes Care* 1995; **18:** 1294–1298.
5 Liese AD, Mayer-Davis EJ, Haffner SM. Development if the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev* 1998; **20:** 157–172.
6 Laakso M, Sarlund H, Salonen R, Suhonen M, Pyörälä K, Salonen JT *et al.* Asymptomatic atherosclerosis and insulin resistance. *Arterioscler Thromb* 1991; **11:** 1068–1076.
7 Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW *et al.* for the Atherosclerosis Risk In Communities (ARIC) Study Investigators. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size and physical activity. *Stroke* 1994; **25:** 166–173.
8 Agewall S, Fagerberg B, Attvall S, Wendelhag I, Urbanavicius V, Wikstrand J. Carotid artery wall intima-media thickness is associated with insulin-mediated glucose disposal in men at high and low cardiovascular risk. *Stroke* 1995; **26:** 956–960.
9 Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R *et al.* for the IRAS Investigators. Insulin sensitivity and atherosclerosis. *Circulation* 1996; **93:** 1809–1817.
10 Rantala AO, Päivänsalo M, Kauma H, Lilja M, Savolainen MJ, Reunanen A *et al.* Hyperinsulinemia and carotid atherosclerosis in hypertensive and control subjects. *Diabetes Care* 1998; **21:** 1188–1193.
11 Bonora E, Tessari R, Micciolo R, Zenere M, Targher G, Padovani R *et al.* Intima-medial thickness of the carotid artery in nondiabetic and NIDDM patients. Relationship with insulin resistance. *Diabetes Care* 1997; **20:** 627–631.
12 Alberti KGMM, Zimmet PZ for the WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. *Diabet Med* 1998; **15:** 539–553.
13 Balkau B, Charles MA for the European Group for the Study of Insulin Resistance (EGIR). Comment on the provisional report from the WHO consultation. *Diabet Med* 1999; **16:** 442–443.
14 Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986; **74:** 1399–1406.
15 Heiss G, Sharett AR, Barnes R, Chambless LE, Szklo M, Alzola C *et al.* Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. *Am J Epidemiol* 1991; **134:** 250–256.
16 Grobbee DE, Bots ML. Carotid artery intima-media thickness as an indicator of generalized atherosclerosis. *J Intern Med* 1994; **236:** 567–573.
17 Bots ML, Hoes AW, Koudstaal PJ, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* 1997; **96:** 1432–1437.
18 Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharett AR *et al.* Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol* 1997; **146:** 483–494.
19 Matthews DR, Hosker JP, Rudsenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28:** 412–419.
20 Berglund G, Elmståhl S, Janzon L, Larsson SA, The Malmö Diet, Cancer Study. Design and feasibility. *J Intern Med* 1993; **233:** 45–51.
21 World Health Organization. *Diabetes Mellitus: Report of a WHO Study Group. Technical Report Series No. 727*. Geneva: World Health Organization, 1985.
22 Taylor HL, Jacobs D, Schuker B, Knudsen J, Leon A, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chron Dis* 1978; **31:** 741–755.
23 Callmer E, Riboli E, Saracci R, Åkesson B, Lindgärde F. Dietary assessment methods evaluated in the Malmö food study. *J Intern Med* 1993; **233:** 53–57.
24 Lean MEJ, Han TS, Seidell JC. Impairment of health and quality of life in people with large waist circumference. *Lancet* 1998; **351:** 863–66.
25 Thorell JI, Larson SM. *Radioimmunoassey and Related Techniques*. St Louis: CV Mosby Company, 1978: 205–211.
26 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18:** 499–502.
27 Wendelhag I, Gustavsson T, Suurkula M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery. Fundamental principles and description of a computerized image analyzing system. *Clin Physiol* 1991; **11:** 565–577.
28 Persson J. *Ultrasound and Atherosclerosis. Evaluation of Methods, Risk Factors and Intervention*. Thesis. Lund University, Lund, Sweden. ISBN 91–628–2673–5, 1997.
29 Berglund G, Riley WA, Barnes RW, Furberg CD. Quality control in ultrasound studies on atherosclerosis. *J Intern Med* 1994; **236:** 581–586.
30 Bots ML, Breslau PJ, Briet E, Bruyn AM de, Vliet HDDM van, VandenOuweland FAM *et al.* Cardiovascular determinants of carotid artery disease. The Rotterdam Study. *Hypertension* 1992; **19:** 717–720.
31 Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 1989; **149:** 1514–1520.

32 Rothman KJ. *Modern Epidemiology*. Boston: Little, Brown & Co, 1986.
33 Salonen R, Salonen HT. Determinants of carotid intima-media thickness: a population based ultrasonography study in Eastern Finnish men. *J Intern Med* 1991; **229:** 225–231.
34 O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK *et al*. on behalf of the CHS Collaborative Group. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke* 1992; **23:** 1752–1760.
35 Harlan WR, Manolio TA. Coronary heart disease. In Marmot M, Elliott P. eds. *Coronary Heart Disease Epidemiology From Aetiology to Public Health*. Oxford: Oxford Medical Publications, 1995:114–126.
36 Wannamethee SG, Sharper AG, Durrington PN, Perry IJ. Hypertension, serum insulin, obesity and the metabolic syndrome. *J Human Hypertens* 1998; **12:** 735–741.
37 Eriksson H, Welin L, Wilhelmsen L, Larsson B, Ohlsson L-O, Svärdsudd K *et al*. Metabolic disturbances in hypertension: results from the population study 'Men born in 1913'. *J Intern Med* 1992; **232:** 389–395.
38 Lindahl B, Asplund K, Hallmans G. High serum insulin, insulin resistance and their associations with cardiovascular risk factors. The Northern Sweden MONICA population study. *J Intern Med* 1993; **234:** 263–270.
39 Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37:** 1595–1607.
40 Meigs JB, D'Augustino RB, Wilson PWF, Cupples LA, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome. The Framingham Offspring Study. *Diabetes* 1997; **46:** 1594–1600.
41 Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G *et al*. Prevalence of insulin resistance in metabolic disorders. The Bruneck Study. *Diabetes* 1998; **47:** 1643–1649.
42 Haffner SM, Gonzales C, Miettinen H, Kennedy E, Stern MP. A prospective analysis of the HOMA model. The Mexico City Diabetes Study. *Diabetes Care* 1996; **19:** 1138–1141.
43 Ferranini E, Mari A. How to measure insulin sensitivity. *J Hypertens* 1998; **16:** 895–906.
44 Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antionio Heart Study. *Diabetes Care* 1997; **20:** 1087–1092.
45 Wooford JL, Kahl FR, Howard GR, McKinney WM, Tolle JF, Crouse JR. Relation of extent of extracranial carotid early atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. *Arterioscler Thromb* 1991; **11:** 1786–1794.
46 ARIC Investigators. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study. 1987–93. *Am J Epidemiol* 1997; **146:** 483–494.
47 O'Leary DH, Polak JF, Kronmal MPH, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999; **340:** 14–22.
48 Hanefeld M, Koehler C, Scharper F, Fuecker K, Henkel E, Temelkova-Kurktschiev T. Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. *Atherosclerosis* 1999; **144:** 229–235.