

HOMA-Estimated Insulin Resistance Is an Independent Predictor of Cardiovascular Disease in Type 2 Diabetic Subjects

Prospective data from the Verona Diabetes Complications Study

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OBJECTIVE — To evaluate whether homeostasis model assessment–estimated insulin resistance (HOMA-IR) is an independent predictor of cardiovascular disease (CVD) in type 2 diabetes.

RESEARCH DESIGN AND METHODS — Conventional CVD risk factors (sex, age, smoking, plasma lipids, blood pressure, and metabolic control) and insulin resistance (estimated by HOMA) were evaluated at baseline in 1,326 patients with type 2 diabetes examined within the Verona Diabetes Complications Study. At baseline and after a mean follow-up of 4.5 years, CVD was assessed by medical history, physical examination, electrocardiography, and echo-Doppler of carotid and lower limb arteries. Death certificates and medical records of subjects who died during the follow-up were carefully scrutinized to identify cardiovascular deaths. In statistical analyses, CVD was an aggregate end point including both fatal and nonfatal coronary, cerebrovascular, and peripheral vascular disease as well as ischemic electrocardiographic abnormalities and vascular lesions identified by echo-Doppler.

RESULTS — At baseline, 441 subjects were coded positive for CVD (prevalent cases). Incident cases numbered 126. Multiple logistic regression analyses showed that, along with sex, age, smoking, HDL/total cholesterol ratio, and hypertension, HOMA-IR was an independent predictor of both prevalent and incident CVD. A 1-unit increase in (log)HOMA-IR value was associated with an odds ratio for prevalent CVD at baseline of 1.31 (95% CI 1.10–1.56, $P = 0.002$) and for incident CVD during follow-up of 1.56 (95% CI 1.14–2.12, $P < 0.001$).

CONCLUSIONS — HOMA-IR is an independent predictor of CVD in type 2 diabetes. The improvement of insulin resistance might have beneficial effects not only on glucose control but also on CVD in patients with type 2 diabetes.

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Accelerated atherosclerosis is a major burden of diabetes. We found that the risk of advanced atherosclerosis (arterial stenosis), the histopathological process underlying most clinical cardio-

vascular events, is fivefold higher in type 2 diabetic subjects than in nondiabetic individuals, even after adjustment for several confounders (1). Therefore, it is not surprising that the risk of coronary heart

disease (CHD), cerebrovascular disease, and peripheral vascular disease is several-fold increased in type 2 diabetes (2) and that CVDs, as a group, represent the leading cause of death in type 2 diabetes (3).

Type 2 diabetes is a complex disease, featured by abnormalities of several risk factors of atherosclerosis, including plasma lipids, blood pressure, and the coagulation cascade (4–6). However, classic risk factors explain only a portion (~25%) of the excess of cardiovascular risk in type 2 diabetes (7). The independent contribution of hyperglycemia was pointed out (8,9), although it is still debated (10). Another culprit could be insulin resistance, which is found in most patients with type 2 diabetes (11,12).

In recent years, several cross-sectional studies documented an independent association between insulin resistance and subclinical or clinical CVD in both nondiabetic (13–15) and diabetic subjects (16,17). However, the most convincing evidences in support of a possible causal, and not coincidental, association between insulin resistance and CVD must come from longitudinal studies and intervention trials. Unfortunately, these evidences are scant. To the best of our knowledge, there is only a full-length paper (18) and a few abstracts based on longitudinal observations of the association between insulin resistance and CVD.

In the present study, we report on the association we found between insulin resistance as estimated by homeostasis model assessment (HOMA) (19) and CVD in a large number of type 2 diabetic patients followed prospectively for ~4.5 years.

RESEARCH DESIGN AND METHODS

Subjects

The Verona Diabetes Complications Study is a longitudinal cohort study initiated in 1988 to identify risk factors of

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiography; HOMA, homeostasis model assessment; HOMA-IR, HOMA insulin resistance score; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

chronic complications in type 2 diabetes. The baseline evaluation included 1,780 subjects randomly recruited among a total of ~25,000 patients, regularly attending the Diabetes Clinics of Verona and surroundings. Patients with major comorbidity and intercurrent illnesses were excluded. The recruitment period lasted 4 years (1 January 1988 to 31 December 1991), and one to two patients were included in the study on each day. A total of 2,000 patients were invited to participate; therefore, the response rate was 89%.

In 1995–1996, a follow-up study was completed, and 1,366 patients were reexamined. Death certificates and medical records of patients who died during the follow-up period were carefully scrutinized to establish the cause of death.

The present report focuses on 960 patients who were not being treated with insulin at baseline and who had complete clinical and biochemical data at baseline and complete cardiovascular data at both baseline and follow-up. The mean follow-up period was 52 ± 0.6 months.

All patients gave their informed consent to participate in the study, which had been approved by the local Ethical Committee.

Clinical data

The following demographic and clinical data were collected with a standardized questionnaire at baseline: sex, age, cigarette smoking, physical activity at work and at leisure, socioeconomic status, previous diseases, and drug consumption. In each subject, the following information about cigarette smoking was recorded: smoking status (nonsmoker, former smoker, and current smoker), average number of cigarettes smoked per day, and number of years of smoking. The level of physical activity during the leisure time was defined using a three-category scale: 1 = no exercise at all; 2 = regular physical activity up to 2 h per week (jogging, biking, swimming, playing tennis, heavy gardening, etc.); 3 = regular physical activity for >2 h per week. The level of physical activity at work was defined using a three-category scale: 1 = sedentary; 2 = moderate; 3 = heavy. The score of physical activity at work and during the leisure time was then averaged to derive a parameter describing overall physical activity.

Weight (to the nearest 0.5 kg) and height (to the nearest 0.5 cm) were measured while the subjects were fasting

overnight and wearing only underwear. BMI was calculated as weight (kg) divided by height (m^2). Subjects with BMI >25 kg/m^2 were categorized as overweight; these subjects included obese individuals (BMI >30 kg/m^2). Waist and hip circumferences (to the nearest 0.5 cm) were measured using a plastic tape meter at the level of the umbilicus and of the greater trochanters, respectively, and waist-to-hip ratio (WHR) was calculated.

Blood pressure was measured with a standard mercury sphygmomanometer on the left arm after at least 10 min of rest. Mean values were determined from two independent measurements. Hypertension was diagnosed according to standard criteria.

Laboratory data

At baseline, in the morning after an overnight fast, venous blood was sampled for the measurement of level of HbA_{1c} and plasma concentration of glucose, total and HDL cholesterol, triglycerides, and insulin. Plasma glucose was measured by a glucose-oxidase method. HbA_{1c} was measured by high-performance liquid chromatography. Plasma total cholesterol, HDL cholesterol, and triglycerides were assessed with standard enzymatic spectrophotometric techniques. Plasma LDL cholesterol was calculated with the equation of Friedewald et al. (20), except when triglycerides exceeded 400 mg/dl (in that case, data were treated as missing). Plasma insulin was measured with radioimmunoassay, of which intra-assay and interassay coefficients of variation were 3.2 and 6.9%, respectively.

Assessment of insulin resistance

In each subject, the degree of insulin resistance was estimated at the baseline by HOMA according to the method described by Matthews et al. (19). In particular, an insulin resistance score (HOMA-IR) was computed with the formula: fasting plasma glucose (mmol/l) times fasting serum insulin (mU/l) divided by 22.5. Low HOMA-IR values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity (insulin resistance). In a previous study, we evaluated the reliability of HOMA by comparison with euglycemic-hyperinsulinemic clamp. HOMA was able to explain 65% of insulin sensitivity measured by glucose clamp, and a misclassification of subjects according to insulin

resistance virtually never occurred. This holds true in both nondiabetic and type 2 diabetic subjects (21).

Assessment of CVD

CVD was assessed both at the baseline and at the follow-up examination as follows. The medical history was collected by a standardized questionnaire administered by a trained physician to record previous or current coronary (e.g., myocardial infarction), cerebrovascular (e.g., stroke), or peripheral (e.g., intermittent claudication) vascular disease. Careful physical examination was performed to identify bruits on the carotid arteries and/or pulses deficit and/or other signs of cerebrovascular or peripheral vascular disease. In subjects with probable or possible arteriosclerosis of carotid and/or lower limb arteries, an echo-Doppler examination was programmed. Patients were coded positive for CVD when plaques were identified. All subjects underwent 12-lead electrocardiography (ECG), which was interpreted according to the Minnesota code (22). The presence of CHD was regarded as “definite” when ECG showed alterations typical of myocardial ischemia (codes 1.1, 4.1, 5.1, 7.1) and/or the proband had a medical history positive for myocardial infarction (chest pain, increased creatine kinase, and typical ECG changes) or angina pectoris (typical effort-dependent chest pain, confirmed by exercise-positive ECG and/or angiography). The presence of CHD was considered “probable” when ECG showed alterations strongly suggestive of ischemia (codes 1.2, 4.2, 5.2) and “possible” when ECG showed alterations suggesting ischemia (codes 1.3, 4.3, 5.3). In patients with probable or possible myocardial ischemia, a thorough cardiological workup was completed to confirm the diagnosis.

Statistical analyses

Statistics were performed using SPSS software and multiple logistic regression analyses. In most of these analyses, CVD was an aggregate end point inclusive of cardiovascular death (myocardial infarction, stroke, other), nonfatal myocardial infarction or stroke, angina pectoris, asymptomatic myocardial ischemia, cerebral transitory ischemic attack, intermittent claudication, gangrene of the lower extremities, and carotid or lower limb arteriosclerosis confirmed by echo-

Table 1—Baseline main clinical and biochemical features of type 2 diabetic patients from the Verona Diabetes Complications Study

	Evaluated at baseline	Reevaluated at follow-up	Reevaluated non-insulin-treated; complete data
<i>n</i>	1,780	1,366	960
Men (%)	49.2	48.2	48.9
Age (years)	64 ± 0.3	64 ± 0.3	64 ± 0.3
Duration of diabetes (years)	9.1 ± 0.2	9.5 ± 0.2	9.3 ± 0.2
Oral agents (%)	78.1	79.8	87.5
Smokers (%)	37.9	39.4	38.1
BMI (kg/m ²)	28.8 ± 0.11	28.9 ± 0.13	28.9 ± 0.14
LDL cholesterol (mmol/l)	3.52 ± 0.03	3.48 ± 0.03	3.49 ± 0.03
HDL cholesterol (mmol/l)	1.27 ± 0.01	1.28 ± 0.01	1.27 ± 0.01
Triglycerides (mmol/l)	1.89 ± 0.03	1.88 ± 0.03	1.74 ± 0.03
Systolic blood pressure (mmHg)	152 ± 0.5	152 ± 0.5	152 ± 0.6
Diastolic blood pressure (mmHg)	88 ± 0.2	88 ± 0.3	88 ± 0.3
Fasting glucose (mmol/l)	8.5 ± 0.05	8.6 ± 0.06	8.4 ± 0.06
Fasting insulin (pmol/l)	111 ± 2	108 ± 2	102 ± 2
HOMA-IR	5.86 ± 0.12*	5.77 ± 0.13†	5.54 ± 0.13
HbA _{1c} (%)	6.5 ± 0.04	6.4 ± 0.05	6.4 ± 0.04

Data are means ± SE. **n* = 1,467; †*n* = 1,164.

Doppler. Separate models focused on prevalent CVD at baseline and incident CVD during follow-up. Several models were tested that included sex, age, duration of diabetes, smoking, physical activity, BMI, WHR, blood pressure, hypertension, LDL cholesterol, HDL cholesterol, total/HDL cholesterol ratio, triglycerides, HbA_{1c}, (log)fasting insulin, and/or (log)HOMA-IR as explanatory variables. Both fixed models and forward stepwise regression models were used. (log)HOMA-IR as well as (log)insulin and HbA_{1c} were modeled as either continuous or categorical variables. Data are presented as means ± SE.

RESULTS—Main clinical and biochemical features of the cohort are summarized in Table 1. Men and women were equally represented; the average age was 64 years, and the mean duration of diabetes was ~9 years. Most subjects were overweight or obese and had dyslipidemia and/or hypertension. The metabolic control was good or fair in most patients, who were mostly treated with oral agents.

At baseline, (log)HOMA-IR was significantly correlated with age ($r = -0.166$, $P < 0.001$), duration of diabetes ($r = -0.206$, $P < 0.001$), BMI ($r = 0.337$, $P < 0.001$), WHR ($r = 0.129$, $P < 0.001$), (log)HDL cholesterol ($r = -0.213$, $P < 0.001$), (log)triglycerides

($r = 0.347$, $P < 0.001$), diastolic blood pressure ($r = 0.149$, $P < 0.001$), fasting glucose ($r = 0.369$, $P < 0.001$), HbA_{1c} ($r = 0.314$, $P < 0.001$), and (log)fasting insulin ($r = 0.948$, $P < 0.001$). The correlations of (log)HOMA with (log)HDL cholesterol, (log)triglycerides, diastolic blood pressure, and HbA_{1c} remained highly significant in multivariate analyses, which allowed for sex, age, and BMI.

At baseline, 585 of 1,780 subjects (33%) were coded positive for CVD (aggregate end point). Of those, 194 (11%) were coded positive for CHD.

At follow-up, 441 of 960 subjects with complete biochemical and cardiovascular data (46%) were coded positive for CVD (aggregate end point). In particular, 258 subjects had clinical or subclinical CHD (27%), 218 had clinical or subclinical cerebrovascular disease (23%), and 129 had clinical or subclinical peripheral vascular disease (13%). Many subjects had vascular disease in multiple sites.

During follow-up of these 960 subjects, 57 deaths due to CVD occurred (34 myocardial infarction and 23 stroke). Of these deaths, 14 occurred in patients who were apparently CVD-free at baseline. Incident CVD disease (new cases during follow-up) was recorded in 126 (20%) of the 627 patients (65% of the cohort) who were apparently free of CVD at baseline. In particular, there were 43 incident nonfatal cases of CHD, 58 incident nonfatal cases of cerebrovascular disease, and 49 incident nonfatal cases of peripheral vascular disease. These cases included asymptomatic carotid or peripheral arteriosclerosis as suspected by physical examination and confirmed by echo-Doppler.

Sex, age, smoking, total/HDL cholesterol ratio, hypertension, and (log)HOMA-IR were independent predictors of prevalent CVD at the baseline (aggregate end point). Similar results were found with forward stepwise multiple regression models (Table 2) or fixed models (not shown). Moreover, results were not different when (log)HOMA-IR was modeled as a continuous variable or as a categorical variable. In particular, baseline

Table 2—Independent predictors of cardiovascular disease (aggregate end point) in type 2 diabetic patients from the Verona Diabetes Complications Study

	OR (95% CI)	<i>P</i> value
Prevalent CVD at the baseline (<i>n</i> = 1,326)		
Sex (men versus women)	1.59 (1.20–2.11)	<0.001
Age (per year)	1.06 (1.04–1.07)	<0.001
Smoking (yes versus no)	1.41 (1.06–1.87)	0.017
Total/HDL cholesterol (per unit)	1.13 (1.05–1.22)	0.002
Hypertension (yes versus no)	1.34 (1.04–1.75)	0.024
(log)HOMA-IR (per unit)	1.31 (1.10–1.56)	0.002
Incident CVD during the follow-up (<i>n</i> = 627)		
Age (per year)	1.04 (1.02–1.06)	<0.001
Smoking (yes versus no)	1.53 (1.00–2.35)	<0.001
Total/HDL cholesterol (per unit)	1.22 (1.06–1.39)	<0.001
(log)HOMA-IR (per unit)	1.56 (1.14–2.12)	<0.001

Sex, duration, BMI, hypertension, and HbA_{1c} did not enter the equation.

CVD risk increased by 31% per each unit increase in (log)HOMA-IR (Table 2), and the odds ratio (OR) for CVD was 1.48 (95% CI 1.02–2.14, $P = 0.037$) in top versus bottom quartile of (log)HOMA-IR. Duration of diabetes, BMI, and HbA_{1c} did not rank among the independent predictors of prevalent CVD at baseline in any of the models we tested. Further multivariate analyses focusing separately on baseline CVD in different sites showed that (log)HOMA was an independent predictor of baseline CHD (OR 1.61, 95% CI 1.24–2.09, $P < 0.001$), whereas baseline cerebrovascular or peripheral vascular disease at baseline were not significantly predicted by (log)HOMA-IR due to low statistical power.

Table 2 also shows the independent predictors of incident CVD (aggregate end point) during the follow-up. Age, smoking, total/HDL cholesterol ratio, and HOMA-IR turned out to be independently associated with incident CVD. Sex, BMI, duration, hypertension, and HbA_{1c} did not enter the forward stepwise multiple regression equation. Similar results were found when these variables were forced into fixed models. Noteworthy, CVD risk increased by 56% per each unit increase in (log)HOMA-IR (Table 2). The OR for incident CVD was 2.74 (95% CI 1.45–5.19, $P = 0.002$) in top versus bottom quartile of (log)HOMA-IR. Due to low statistical power, (log)HOMA-IR was not a significant predictor of incident CHD, cerebrovascular disease, or peripheral vascular disease when these end points were examined separately.

When (log)fasting insulin replaced (log)HOMA-IR in the multivariate models, it was significantly associated with prevalent CVD at baseline (OR 1.54, 95% CI 1.27–1.88, $P < 0.001$ per each unit increase; 1.85, 1.31–2.61, $P < 0.001$ in top versus bottom quartile) but not to incident CVD during follow-up.

When systolic or diastolic blood pressure replaced hypertension in the various models, the results did not change. When (log)HOMA-IR was excluded from the models, BMI and duration of diabetes did not turn out to be independent predictors of prevalent CVD at the baseline or of incident CVD during follow-up. In these models, exclusion of (log)HOMA-IR permitted HbA_{1c} to rank among the independent predictors of prevalent CVD at baseline (1.44, 1.04–1.99, $P = 0.028$ in top versus bottom quartile) and incident

CVD during follow-up (2.03, 1.13–3.69, $P = 0.019$), along with sex, smoking, and total/HDL cholesterol ratio.

In further analyses, we separately tested multiple regression models including or excluding variables most strictly related to insulin resistance. When models included sex, age, duration of diabetes, smoking, LDL cholesterol, hypertension, and (log)HOMA-IR, the latter was an independent predictor of prevalent CVD at baseline (1.34, 1.12–1.59, $P < 0.001$) as well as incident CVD during follow-up (1.57, 1.16–2.20, $P = 0.003$). When models also included physical activity, BMI, WHR, HDL cholesterol, triglycerides, and HbA_{1c}, which are strongly related to insulin resistance, (log)HOMA-IR was still associated with prevalent CVD at baseline (1.51, 1.20–1.89, $P < 0.001$) and marginally with incident CVD during follow-up ($P = 0.060$).

When subjects were stratified according to BMI, HbA_{1c}, and duration of diabetes, (log)HOMA-IR proved itself to be an independent predictor of prevalent CVD at baseline in subjects both below (1.35, 1.05–1.74, $P = 0.018$) and above the median of BMI (1.42, 1.10–1.83, $P = 0.006$), in those both below (1.39, 1.08–1.79, $P < 0.011$) and above the median of diabetes duration (1.30, 1.03–1.65, $P = 0.027$), as well as in subjects above the median of HbA_{1c} (1.32, 1.04–1.69, $P = 0.022$). In subjects below the median of duration of diabetes, (log)HOMA-IR was also a predictor of incident CVD during follow-up (OR 1.62, CI 1.02–2.58, $P < 0.001$).

CONCLUSIONS— Insulin resistance is a hallmark of type 2 diabetes (23) that precedes and predicts the disease for several years (26). In nondiabetic as well as diabetic subjects, insulin resistance is related to several cardiovascular risk factors, including hyperglycemia (12), dyslipidemia (12), hypertension (12,25), thrombophilia (26), and cigarette smoking (27). For such reasons, insulin resistance might be regarded as an accomplice in the pathogenesis of CVD in type 2 diabetes. Nevertheless, it is interesting to establish whether insulin resistance does contribute to atherosclerosis and CVD also through a sort of shortcut, i.e., a direct and independent pathway. This information would be of great clinical value, because it might strongly justify and encourage the use of therapeutic options,

including drugs capable of improving insulin sensitivity, with the aim of reducing the cardiovascular risk. In this context, it is important to remember that physical activity, which improves insulin sensitivity, was shown to prevent CVD in patients with type 2 diabetes (28). Moreover, administration of metformin, a drug that is effective for insulin resistance (29), was the only therapeutic approach successful in reducing the incidence of myocardial infarction in the U.K. Prospective Diabetes Study (30). Finally, an insulin-sensitizing agent such as troglitazone was able to reduce intima-media thickness in type 2 diabetic patients (31).

In the present study, we found that insulin resistance, as estimated by HOMA (19), was a strong predictor of both prevalent CVD at baseline and incident CVD during follow-up in a large sample of type 2 diabetic subjects participating in the Verona Diabetes Complications Study. This was found independently of classic risk factors (e.g., smoking) and variables most strictly related to insulin resistance (e.g., BMI). As expected, smoking, total/HDL cholesterol ratio, hypertension, and poor metabolic control were the other predictors of CVD. Therefore, it seems that insulin resistance can strongly contribute to the more devastating chronic complication of type 2 diabetes through a pathway that is distinct from those involving many classic risk factors. This finding supports the idea that insulin resistance in type 2 diabetes deserves specific treatment targeting not only hyperglycemia but also CVD.

In this study, we did not use the gold standard in assessment of insulin sensitivity, i.e., the glucose clamp (32). However, other investigators and ourselves (19,21,33) reported that HOMA-IR is strongly related to clamp-measured insulin resistance in both nondiabetic and diabetic subjects. In the latter, we found that the coefficient of correlation of HOMA-IR with insulin-stimulated total glucose disposal during insulin clamp ($r = -0.695$) was similar to that measured in nondiabetic subjects ($r = -0.745$) (21). Consistent results were found in diabetic subjects by Emoto et al. (33). In our study, we also found that a misclassification of subjects according to insulin resistance is very rare with HOMA in both nondiabetic and diabetic subjects (21). Therefore, HOMA seems to be a reliable tool in the assessment of insulin re-

sistance, which can be used as a valid alternative to the glucose clamp or other sophisticated techniques in epidemiological settings. Indeed, longitudinal studies of large samples are not feasible with the glucose clamp.

Our results are consistent with those of several cross-sectional studies performed in both nondiabetic and diabetic subjects. These studies, which were carried out with a variety of methods, including the glucose clamp, the intravenous glucose tolerance test with the minimal model, the insulin suppression test, and the short intravenous insulin tolerance test, consistently documented that subjects with coronary, cerebrovascular, or peripheral atherosclerosis are less insulin sensitive than subjects without atherosclerosis (13–17). Furthermore, our results are in agreement with the few longitudinal studies exploring the association of insulin resistance with CVD. Among the latter, only one study was published as a full-length paper (18), whereas the others are abstracts. Nevertheless, these studies support the conclusion that insulin resistance predicts subsequent CVD.

Also, hyperinsulinemia, another surrogate marker of insulin resistance, was able to predict CVD in several studies (34–36). However, other studies failed to find a significant association between plasma insulin and CVD (37,38) or complex associations (39). Moreover, most of these studies focused on samples from the general population and not on diabetic patients. Also, the ability of the β -cell to respond to insulin resistance with an increase in hormone secretion is disrupted in type 2 diabetes; therefore, hyperinsulinemia is not as good a marker of insulin resistance as in subjects with normal glucose tolerance.

Although establishing the pathophysiologic pathways linking insulin resistance to CVD in type 2 diabetes is beyond the scope of the present study, it seems not out of place to mention that a number of mechanisms were identified through which an impaired insulin sensitivity could result in atherosclerosis. These mechanisms include the antiaggregating platelet effect of insulin (40), the effect of the hormone on nitric oxide release from the endothelium (41), the inhibition by insulin of migration of vascular smooth muscle cells (42), and the inhibitory effect of the hormone on fibrinogen synthesis

(43). These potentially antiatherogenic properties of insulin seem to be impaired in insulin-resistant states such as type 2 diabetes (44,45), and this might contribute to explain our results. Alternatively, one might argue that some of the several biological processes modulated by insulin could not be impaired in insulin-resistant states and that hyperinsulinemia, which generally coexists with insulin resistance, might promote atherosclerosis. In fact, it has been found that insulin possesses potentially proatherogenic effects. The hormone enhances LDL cholesterol susceptibility to oxidation (46), promotes plasminogen activator inhibitor 1 (47) and endothelin-1 (48) release by several cells, and stimulates connective matrix and cholesterol synthesis and LDL receptor expression in the arterial wall (49). A third hypothesis is that the increased atherosclerosis observed in insulin-resistant states such as type 2 diabetes could stem from the perverse combination of the deficiency of antiatherogenic effects of insulin, on the one side, and the presence of proatherogenic effects of hyperinsulinemia on the other side. Of course, such a hypothesis requires that insulin resistance could be a selective phenomenon that differently impairs the pathways leading to atherosclerosis and that the hormone possesses both proatherogenic (e.g., the stimulus of plasminogen activator inhibitor 1 synthesis) and antiatherogenic (e.g., stimulus of nitric oxide synthesis) biological effects. This hypothesis, if confirmed, would reconcile the results of the epidemiological studies, supporting the idea that insulin is a proatherogenic hormone (34–36), and the results of studies like ours, giving strength to the conclusion that insulin is an antiatherogenic hormone. Interestingly, however, both hyperinsulinemia and insulin resistance precede type 2 diabetes of several years (33,50), and many type 2 diabetic patients have CVD at the time when the disease is first diagnosed (50).

One might argue that because a screening of carotid and peripheral arteriosclerosis with echo-Doppler was not performed in all subjects examined in the present study, some of the patients with significant vascular lesions could remain undetected. This might be true. However, we do not believe that the failure of identifying a number of subjects with subclinical arteriosclerosis could have made our results unreliable. In fact, false-negative

patients, if any, might have led to an underestimation rather than an overestimation of the association of insulin resistance with CVD.

In conclusion, the present study suggests that HOMA-IR is an independent risk factor of CVD in type 2 diabetes. Therefore, therapeutic options capable of ameliorating or reversing insulin resistance might be considered in the treatment of these patients, most of whom will experience CVD events during their life. These options might result in both the control of hyperglycemia and the prevention of CVD by acting on the common roots of diabetes and atherosclerosis. The results of trials specifically addressing the effect of insulin-sensitizing drugs on the incidence of CVD in type 2 diabetes are awaited.

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