Intimal-Medial Thickness of the Carotid Artery in Nondiabetic and NIDDM Patients

Relationship with insulin resistance

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OBJECTIVE — The aim of this study was *1)* to compare intimal-medial thickness (IMT) of the carotid artery in nondiabetic and NIDDM patients and *2)* to evaluate the association of this early marker of atherosclerosis with several cardiovascular risk factors, including plasma insulin and insulin resistance.

RESEARCH DESIGN AND METHODS — A total of 58 nondiabetic and 56 NIDDM patients, randomly selected among those attending the outpatient Diabetes Clinic or the Clinic for Internal Medicine were examined. BMI, waist-to-hip ratio (WHR), blood pressure, glycohemoglobin (HbA_{1c}), and fasting concentrations of plasma glucose, serum lipids (total and HDL cholesterol, triglycerides), and serum insulin were measured. Insulin resistance was assessed by computing glucose disappearance rate from plasma after intravenous insulin injection (K_{itt}). IMT of the carotid artery was measured by ultrasonography.

RESULTS — IMT was significantly higher in diabetic patients, and the difference remained highly significant after adjusting for sex, age, BMI, WHR, presence of hypertension and dyslipidemia, and smoking status (1.39 vs. 1.24 mm, common SD 0.12, $P < 0.001$). Univariate regression analyses showed that IMT was negatively correlated with K_{itt} in either nondiabetic ($r = -0.348$, $P < 0.01$) or diabetic patients ($r = -0.492$, $P < 0.001$). However, multiple regression analyses showed that IMT was independently associated with age and WHR in nondiabetic subjects, whereas in diabetic patients, IMT was independently predicted by K_{itt} and hypertension. These two variables explained ~62% and ~35% of the variability of IMT in nondiabetic and diabetic patients, respectively. Plasma insulin was not independently associated with IMT in either groups.

CONCLUSIONS — These results indicate that *1)* diabetes is characterized by a greater thickness of the carotid artery independently of other established risk factor of atherosclerosis, *2)* early atherosclerosis is independently associated with insulin resistance in diabetic but not in nondiabetic patients, *3)* central adiposity is an independent predictor of IMT in nondiabetic individuals.

About 15 years ago epidemiological prospective studies (Paris Prospective Study, Busselton Study, and Helsinki Policemen Study) reported that hyperinsulinemia can predict coronary heart disease, independently of the presence of diabetes, dyslipidemia, and hypertension (1–3). Despite several inconsistencies within and between these studies, especially in extended follow-up examinations (4–7), and the presence in the literature of several articles disputing the independent association between insulin and atherosclerosis (8), data from Paris, Busselton, and Helsinki studies are frequently quoted to support the concept that hyperinsulinemia should be included among cardiovascular risk factors (9). On the other hand, this conclusion is substantiated by a recent case-control study (10), and by several experiments carried out in vitro or in animal models. These experiments suggest a direct effect of insulin on atherogenesis (11).

Hyperinsulinemia generally underlies insulin resistance, of which hyperinsulinemia is a compensatory mechanism aimed mainly at maintaining an intact glucose homeostasis (12). This assumption led to the hypothesis that what is true for hyperinsulinemia, according to the transitive property, might be valid also for insulin resistance. In particular, it has been suggested that insulin resistance might be the true pathogenetic risk factor of atherosclerosis, and that hyperinsulinemia might be just a marker of insulin resistance, without any causal relationship with atherosclerosis (13,14). At present, however, it is not clear whether this hypothesis rests on solid arguments, because only a few studies have examined the relationships existing between insulin resistance and atherosclerosis (15,16).

In the present study we compared intimal-medial thickness (IMT) of the common carotid artery, i.e., a reliable indicator of early atherosclerosis (17), in nondiabetic and NIDDM patients and tested the hypothesis that insulin resistance, as assessed by glucose disappearance rate from plasma after intravenous insulin injection, is related to IMT independently of several established risk factors of atherosclerosis.

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IMT, intimal-medial thickness; IRAS, Insulin Resistance and Atherosclerosis Study; K_{itt}, coefficient of glucose disappearance from plasma after intravenous insulin; WHR, waist-to-hip ratio.

RESEARCH DESIGN AND METHODS

Subjects

After informed consent was obtained, 114 subjects were studied: 58 were nondiabetic and 56 had NIDDM according to conven-

tional criteria (18). In particular, age at diagnosis was >40 (mean ± SD, 52 ± 6), ketosis had never occurred, and insulin had never been necessary for treatment in any diabetic patient. The patients were randomly recruited among outpatients attending the Diabetes Clinic or the Clinic for Internal Medicine of the Hospital of Negrar (Verona, Italy) after the exclusion of: *1)* insulin-treated diabetic patients, *2)* subjects suffering from chronic diseases or taking medications known to affect glucose and/or insulin metabolism, *3)* subjects who had experienced clinical manifestation of cardiovascular disease, *4)* subjects who had participated in dietary or exercise programs for weight reduction during the 2 weeks before the study. In all subjects, standard electrocardiogram was normal, no bruit was present on carotid arteries, and no major evidence of peripheral vascular disease was present. Among diabetic patients, 18 were treated with diet only, 11 with metformin, 18 with sulphonylureas, and 9 with commercial associations of biguanides and sulfonylureas. Nondiabetic patients had been referred to the outpatient Clinic for Internal Medicine because of hypertension (n = 19), dyslipidemia (n = 12), hyperuricemia (n = 7), obesity (n = 6), recurrent abdominal pain (n = 9), or tachyarrhythmias (n = 5). Current smoking status was ascertained, and subjects were classified as cigarette smokers and nonsmokers.

Anthropometric data

All subjects were examined while wearing only underwear. Height (to the nearest 0.5 cm) and weight (to the nearest 0.5 kg) were recorded. BMI was calculated as weight divided by height squared. Waist circumference (widest between the lower rib margin and the iliac crest) and hip circumference (widest over the great trochanters) were measured in duplicate, and the values were averaged. Waist-to-hip ratio (WHR) was calculated and used as an index of regional fat distribution, higher values documenting a central adiposity or obesity.

Blood pressure

Blood pressure was measured with a standard mercury sphygmomanometer on the right arm, after the subjects had been seated for at least 10 min. Mean values were determined from two independent measurements taken at 5-min intervals. Hypertension was defined by a systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg or when an antihypertensive treatment was in progress (19).

Insulin sensitivity

Insulin sensitivity was assessed by computing the glucose disappearance rate from plasma after intravenous insulin injection, as previously described (20). Briefly, at 08:00–08:30 A.M., after an overnight fast, 0.1 U/kg body weight of regular insulin (Humulin R, Eli Lilly, Indianapolis, IN) was given intravenously as a bolus, and blood samples were collected before and 3, 6, 9, 12, and 15 min after insulin adminsitration. The rate constant for plasma glucose disappearance (K_{itt}) was calculated from the formula $0.693/t_{1/2}$. The plasma glucose $t_{1/2}$ was calculated from the slope of least-squares analysis of the plasma glucose concentrations from 3–15 min after intravenous insulin injection. This method allows the ranking of subjects according to their degree of sensitivity to insulin or, reciprocally, to their degree of insulin resistance. The method gives results strongly correlated with those derived from euglycemic hyperinsulinemic clamp, as reported by other investigators (21) and ourselves (20) in either young or older subjects.

Lipids, glucose, glycohemoglobin, and insulin

The basal sample of the intravenous insulin test was used for determination of serum total and HDL cholesterol, triglycerides as well as insulin. Plasma glucose and serum lipids were measured by standard enzymatic methods, glycohemoglobin by high performance liquid chromatography, and serum insulin by double-antibody radioimmunoassay. Serum LDL cholesterol was calculated with the equation of Friedewald et al. (22), except when triglycerides were >400 mg/dl. Dyslipidemia was considered to be present when patients had serum total cholesterol >240 mg/dl (23) and/or triglycerides >250 mg/dl (24) and/or HDL cholesterol <40 mg/dl in women and <35 mg/dl in men.

Carotid sonography

In all participants, a carotid sonography was performed with high-resolution B-mode scanning equipment (Sonos 1000, Hewlett-Packard), with a 7.5-MHz sector scanner probe. All exams were carried out by a single specialist physician, and all images were photographed. The IMT of the carotid artery was measured as the distance from the leading edge of the first echogenic line, corresponding to the lumen-intimal interface, to that of the second echogenic line, corresponding to the collagen-contained upper layer of tunic adventitia (17). The measurement of IMT was made in the 1-cm segment proximal to the dilation of the carotid bulb and always in plaque-free segments. For each patient, three measurements on both sides were performed, on the anterior, lateral, and posterior projection of the near and far wall. All readings were then averaged.

Statistical analysis

Student's t test for unpaired data was used for comparing mean values of selected variables in diabetic and nondiabetic patients, whereas the χ^2 test was used for comparing proportions.

Analysis of covariance was used to compare mean values of IMT in diabetic and nondiabetic patients after adjustment for other variables (sex, age, BMI, WHR, dyslipidemia, hypertension, smoking).

Simple (Pearson's) correlation coefficients between IMT and selected variables were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with IMT. These analyses were carried out separately in nondiabetic and diabetic patients. Mode of diabetes treatment was included in the regression model used in diabetic patients. A significance level of 0.05 was always used.

RESULTS — Table 1 summarizes the mean values of main clinical features in the whole sample, as well as in nondiabetic and diabetic patients. Sex distribution was not different in the two subgroups. Age was slightly, but significantly higher in diabetic than in nondiabetic patients; the former also showed higher BMI and WHR, lower serum levels of HDL cholesterol, higher concentrations of serum triglycerides, and higher values of blood pressure. Smokers were similarly represented in the two groups. Fasting serum insulin was higher in diabetic than in nondiabetic patients, whereas K_{itt} (i.e., insulin sensitivity) was lower in diabetic than in nondiabetic patients.

IMT was significantly higher in diabetic than in nondiabetic patients (1.44 ± 0.15 vs. 1.19 ± 0.15 mm, $P < 0.001$). This difference remained significant after adjusting for sex, age, BMI, WHR, smoking status, and presence of dyslipidemia and hypertension (1.39 vs. 1.24 mm, common SD 0.12, $P < 0.001$).

Table 1—*Main clinical features of patients in study*

	Nondiabetic patients	Diabetic patients
n	58	56
Men	75.9	73.2
Age (years)	50.0 ± 14.3	56.9 ± 8.2*
BMI (kg/m²)	24.8 ± 3.6	29.4 ± 4.4†
WHR	0.96 ± 0.07	1.05 ± 0.08†
Smokers	44.6	50.0
Fasting glucose (mmol/l)	4.90 ± 0.69	7.65 ± 2.1†
GHb (%)	4.2 ± 0.7	6.5 ± 1.6†
Total cholesterol (mmol/l)	4.96 ± 1.19	5.04 ± 1.15
HDL cholesterol (mmol/l)	1.26 ± 0.32	1.11 ± 0.26*
Triglycerides (mmol/l)	1.41 ± 0.68	1.85 ± 0.86*
Dyslipidemic	25.9	62.5†
Systolic blood pressure (mmHg)	141 ± 25	153 ± 20*
Diastolic blood pressure (mmHg)	84 ± 14	87 ± 11
Hypertensive	36.2	60.7†
Fasting insulin (pmol/l)	64 ± 37	117 ± 50†
K_{itt} (%/min)	3.74 ± 1.05	2.35 ± 0.82†

Data are *n*, %, or means ± SD. *$P < 0.01$; †$P < 0.001$.

In nondiabetic patients, IMT was significantly correlated with age ($r = 0.707$, $P < 0.001$), BMI ($r = 0.369$, $P < 0.01$), WHR ($r = 0.593$, $P < 0.001$), hypertension ($r = 0.381$, $P < 0.01$), and K_{itt} ($r = -0.348$, $P < 0.01$). In diabetic patients, IMT was significantly correlated with hypertension ($r = 0.413$, $P < 0.01$) and K_{itt} ($r = -0.492$, $P < 0.001$).

Multiple regression analyses were carried out in the two groups by using the step-wise procedure. These analyses included IMT as a dependent variable and candidate risk factors (sex, age, BMI, WHR, smoking, dyslipidemia, hypertension, K_{itt}, and insulin) as independent variables. As shown in Table 2, the final "best fitting" model was different in nondiabetic and diabetic patients. In the former, age and WHR were independently associated with IMT and, together, explained 62.4% of its variability. In diabetic patients, IMT was independently predicted by hypertension and K_{itt}, which explained 35.3% of IMT variability. Other variables, including sex, BMI, smoking, dyslipidemia, and fasting insulin, were not independently associated with IMT in either nondiabetic or diabetic patients.

CONCLUSIONS — As reported by several authors, including ourselves, hyperinsulinemia is associated with most major risk factors for atherosclerosis (25–31) and, through the adverse pathogenic effects of these factors, it undoubtedly subtends an increased cardiovascular risk. Furthermore, hyperinsulinemia seems to be an independent risk factor of coronary heart disease (1–3,10). Accordingly, it has been recently reported that fasting serum insulin is independently related to carotid artery thickness (32).

Because hyperinsulinemia generally underlies insulin resistance (12), the hypothesis that insulin resistance rather than hyperinsulinemia might be the true risk factor for atherosclerosis has been formulated (13,14). Consistent with such hypothesis, in both diabetic and nondiabetic patients, it has been found that either coronary heart disease or extracoronary vascular disease is associated with insulin resistance (15,16,33–35).

Our present data confirm that diabetic patients have an IMT greater than nondiabetic individuals (36,37) and give further support to the concept that in nondiabetic patients, age is a strong independent predictor of carotid atherosclerosis (32,36–38). In addition, our data indicate that in nondiabetic patients, a central pattern of fat distribution is associated with carotid atherosclerosis independently of established risk factors. The association between WHR and carotid thickness is in agreement with the results reported by Welin et al.(39), who found that WHR is an independent predictor of stroke, and with those reported by Folsom et al. (32), who measured IMT of carotid arteries in a very large sample of adults (32).

As to the relationship between IMT and insulin sensitivity, we were able to find a simple (univariate) negative association in both diabetic ($r = -0.492$, $P < 0.001$) and nondiabetic patients ($r = -0.348$, $P < 0.01$). However, multiple regression analysis showed that insulin resistance was a predictor of IMT independent of several possible confounders like sex, age, BMI, WHR, smoking, insulin, hypertension, and dyslipidemia, including high triglycerides, only in diabetic patients.

To our knowledge, only one published report has focused on the relation existing between the degree of insulin resistance and IMT, i.e., early atherosclerosis (40). In that report, the investigators of the Insulin Resistance and Atherosclerosis Study (IRAS) found that IMT of either common or internal carotid artery was negatively associated with insulin sensitivity, as assessed by the frequently sampled intravenous glucose tolerance test with analysis by the minimal model. The relationships were independent of sex, age, total and HDL cholesterol, hypertension, and smoking. However, when glucose tolerance, BMI, WHR, and fasting insulin were included in the multiple regression models, IMT was no longer sta-

Table 2—*Final results of step-wise multiple regression analyses carried out with IMT of carotid artery as dependent variable and sex, age, BMI, WHR, cigarette smoking, K_{itt}, insulin, diabetes, dyslipidemia, and hypertension as independent variables*

Variable	β coefficient	SE	*t*	*P*
Nondiabetic patients				
Constant	0.115	0.180	—	—
Age	0.005623	0.000925	4.09	<0.001
WHR	0.817	0.200	4.09	<0.001
Diabetic patients				
Constant	1.573	0.061	—	—
K_{itt}	−0.081	0.021	3.79	<0.001
Hypertension	0.106	0.036	2.96	0.005

tistically associated with insulin resistance. Noteworthy, in this study plasma triglycerides were not considered in the statistical analysis, and this was extensively criticized (41). In addition, in the IRAS insulin sensitivity could not be measured in ~15% of individuals, mainly diabetic patients, due to limitations intrinsic to the methodology used to assess the parameter. Thus, we believe that our data, which included triglycerides in the statistical analyses and which were obtained by a method to assess insulin sensitivity that gave valid measurements in all individuals examined, provide a useful integration of the results reported by the investigators of the IRAS (40).

The relationship we have found between insulin resistance and carotid wall thickness in diabetic patients is consistent with the observation of a more severe degree of insulin resistance in diabetic patients with coronary heart disease (33). Interestingly, this relationship was found after controlling for abnormalities known to cluster with insulin resistance and that are risk factors of atherosclerosis (obesity, central fat distribution, hypertension, dyslipidemia). As a consequence, it might be concluded that insulin resistance is related to carotid atherosclerosis in diabetic patients independently of established risk factors. Whether this independent statistical association subtends a cause-effect relationship remains to be elucidated. However, there is evidence in the recent literature suggesting that an impaired insulin action on several cells involved in the atherosclerotic process (platelets, monocytes-macrophages, endothelial cells, vascular smooth muscle cells, fibroblasts) might contribute to the development of atherosclerosis (42–45).

The failure to find an independent association of IMT with insulin resistance in nondiabetic patients is consistent with data obtained in the IRAS when all possible confounders were included in the multivariate analyses (40). Nevertheless, the discrepancy we have found in this association between diabetic and nondiabetic patients is not easy to explain. It might be postulated that insulin resistance is able to contribute significantly to IMT only when the metabolic abnormality is as severe as in diabetic patients. In other words, it might be that insulin resistance subtends one or more cell derangements, favoring atherosclerosis only in diabetic individuals. As an alternative hypothesis, the lack of independent association between K_{itt} and IMT might just depend on the tangled web that ties insulin sensitivity with almost all risk factors of atherosclerosis (14,30), which makes statistical analyses difficult to perform and interpret. As a matter of fact, a common finding in multivariate analyses is that a variable that is predictive when considered alone in univariate analysis drops out when other covariates are considered in the more complex multivariate model. In our study, for instance, K_{itt} was a significant predictor of IMT in nondiabetic patients in univariate but not in multivariate analysis. This might mean simply that K_{itt} does not contribute significantly to the optimum predicting model for that data set but it does not necessarily mean that insulin resistance has no independent role in the development of atherosclerosis.

In the present study, fasting insulin was not an independent predictor of IMT. This is consistent with the results of several studies challenging the idea that insulin is linearly and independently related to clinical manifestations of atherosclerosis (8), including the very recent IRAS (40).

In conclusion, our results suggest that *1)* diabetes is characterized by a greater thickness of the carotid artery independently of other established risk factors of atherosclerosis, *2)* early atherosclerosis is independently associated with insulin resistance in diabetic but not in nondiabetic patients, *3)* central adiposity is an independent predictor of IMT in nondiabetic individuals.

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