Insulin resistance is associated with increased risk of major cardiovascular events in patients with preexisting coronary artery disease

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Background Over the past years it has been recognized that insulin resistance (IR) is an independent risk factor for the development of diabetes, whereas its association with cardiovascular events remains controversial. The aim of our study was to explore the association between IR per se and cardiovascular events among patients with preexisting coronary artery disease.

Methods The mean follow-up period of this prospective study was 6.2 years. Metabolic and inflammatory parameters were analyzed from stored frozen plasma samples obtained at baseline from 2938 patients aged 45 to 74 years. The homeostatic index of IR (HOMA-IR) was calculated according to the homeostasis model assessment.

Results New major cardiovascular events (fatal and nonfatal myocardial infarction and sudden death) were recorded in 108 (11.1%) patients from the lowest IR tertile, in 147 (14.7%) from the intermediate tertile, and in 166 (17.2%) from the highest tertile ($P = .0002$). The linear trend for total and cardiac death across the tertiles of HOMA-IR was significant as well ($P = .02$ and $P = .009$, respectively). The highest age-adjusted rates for major cardiovascular events and new diabetes were found among patients within the top tertile of HOMA-IR (57% and 130% higher rates, respectively, tertile 3 vs tertile 1, $P < .0001$ for both). Multivariable analysis identified HOMA-IR (tertile 3 vs tertile 1) as an independent predictor of increased risk of major cardiovascular events and new diabetes with hazard ratios (95% CI) of 1.4 (1.1-1.8) and 1.5 (1.1-2.0), respectively.

Conclusions Insulin resistance per se is an independent risk factor for cardiovascular events and new diabetes in patients with preexisting coronary artery disease. (Am Heart J 2007;153:559-65.)

Over the past years it has been recognized that insulin resistance (IR) is an independent risk factor for the development of type 2 diabetes mellitus,[1-3] whereas its association with major cardiovascular events remains controversial.[4-14]

Because the components of the IR syndrome are independent cardiovascular disease risk factors, it could be expected that patients with this syndrome are at higher risk of cardiovascular events. However, whether IR per se is an independent risk factor for major cardiovascular events, particularly in the diverse clinical conditions, remains uncertain.

In the general population, the prognostic value of IR for cardiovascular events was demonstrated.[9-13] In contrast, among patients with type 2 diabetes mellitus, IR probably is not a risk factor for cardiovascular disease.[4] Furthermore, IR and hyperinsulinemia were not independently associated with the development of cardiovascular disease in part of prospective studies among the elderly[6,7] as well as in nondiabetic native American[5] and Asian Indian subjects.[8] The possible association of IR per se with major cardiovascular events in patients with preexisting coronary artery disease (CAD) remains to be established. Therefore, the aim of our study was to explore the risk prediction of cardiovascular events conferred by IR per se among patients with preexisting CAD enrolled in the BIP study.

Methods

Subjects

The major inclusion and exclusion criteria for the BIP study, as well as the ethical guidelines, have been previously

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reported.[15,16] In brief, inclusion criteria for men and women comprised age of 45 to 74 years; history of MI >6 months and <5 years before enrollment into the study; and/or stable angina supported by coronary angiography, and/or radionuclear studies, or standard exercise tests. In addition, lipid profile of serum total cholesterol between 180 and 250 mg/dL, low-density lipoprotein cholesterol level of 180 mg/dL (160 mg/dL for patients <50 years old), high-density lipoprotein cholesterol (HDL-C) level of 45 mg/dL, and triglyceride level of 300 mg/dL were required. The major exclusion criteria for the BIP study were permanent pacemaker implantation, cerebrovascular disease, chronic hepatic or renal disease, peripheral vascular disease, malignant diseases, estrogen replacement therapy, insulin-dependent diabetes mellitus, and current use of a lipid-modifying drug. The study was a multicenter prospective trial performed in 18 university-affiliated hospitals. The trial was approved by the Helsinki committee of each center and the central national Helsinki committee.

There were 3122 eligible patients who were included in the main BIP study. Among them, data were missing in 184 regarding level of blood fasting glucose and/or insulin: all of these patients were excluded from this analysis. Thus, the final study sample for the current analysis comprised 2938 patients.

The patients received either 400 mg of bezafibrate retard or placebo once a day. Patients continued their prescribed medications for cardiac and other conditions except for lipid-lowering drugs. Routine visits to the clinics were scheduled bimonthly for study medication distribution and compliance assessment by tablet count and every 4 months for clinical evaluation. During the 4-month visit, data on any adverse events (as defined in the study protocol), hospitalizations, and study outcomes were obtained. Lipid profiles, fibrinogen levels, and metabolic and safety parameters were measured in the central laboratory at randomization, at 4 months, and annually thereafter until the end of the study. An independent critical event committee, whose members were blinded to the treatment assignment, reviewed primary end points and all-cause mortality. The primary end point of the study was fatal myocardial infarction (MI), nonfatal MI, or sudden death (occurring within 24 hours of onset of symptoms). The follow-up period of the BIP study lasted until May 1998 (mean 6.2 ± 0.8 years, range 4.7-7.6 years). The primary end point of the BIP study was fatal or nonfatal MI or sudden death (combined major cardiovascular events).

Laboratory methods

Detailed data on laboratory methods were given in a previous report.[16,17] A central laboratory performed all biochemical determinations. All samplings at baseline and during follow-up were performed in the fasting state. For the purpose of the present study, plasma citrate samples, which had been taken at baseline from each study participant and stored at −70°C, were thawed and assayed for insulin level by Immulite 2000 analyzer (Diagnostic Products Corporation, Los Angeles, CA) with manufacturer's reagents-solid-phase, 2-site, chemiluminescent enzyme–labeled immunometric assay. This assay uses monoclonal and polyclonal antibodies for the respective capture and detection of insulin. The inter- and intraobserver variabilities of the insulin test in our study were 6.1% and 7.9%, respectively.

The homeostatic indices of IR (HOMA-IRs) were calculated according to the homeostasis model assessment as follows:

$$HOMA-IR = \textit{fasting insulin}\ (\mu U/mL) \cdot \textit{fasting glucose} \times (mmol/L)/22.5\ [\text{or } \textit{fasting glucose} \times (mg/dL)/405]$$

Determination of additional variables

Criteria for the diagnosis of MI, anginal syndrome, hypertension, and congestive heart failure have been previously reported.[16] Smoking habits were determined on the basis of self-report by the patient during an interview held with a study physician. The diagnosis of diabetes at baseline was done by the referring physician and confirmed in the framework of a university hospital based on the reported history and medical records. In addition, in accordance with the American Diabetes Association classification,[18] we defined all patients with fasting blood glucose levels at baseline of ≥126 mg/dL (7 mmol/L) or taking any type of pharmacologic antidiabetic treatment as diabetic patients. There were 431 diabetic patients at baseline. In patients without diabetes at baseline, we defined glucose levels of ≥126 mg/dL (7 mmol/L) during follow-up and/or initiation of any type of pharmacologic antidiabetic treatment as criteria of new diabetes.[19]

Statistical analysis

Data were analyzed using the SAS software (SAS Institute, Cary, NC).[20] Continuous variables at baseline were presented as mean values ± SD. Comparisons between groups were made using χ^2 tests for discrete variables and analysis of variance or Wilcoxon rank sum test for continuous variables.

Kaplan-Meier curves were produced using the LIFETEST procedure. The log-rank test was used for comparing the curves.

To explore the risk of clinical events associated with increasing HOMA-IR, we evaluated the risk of the BIP study primary end point, cardiac death, total death, and development of new diabetes in accordance with tertiles of HOMA-IR at baseline. Multivariable analysis of incidence of the main clinical outcomes (major cardiovascular events and new diabetes) was performed using the Cox proportional hazard model (Cox's proportional-hazards regression model procedure) to account for differing lengths of follow-up and correlation with covariates. Hazard ratio (HR) and 95% CI for new diabetes and major cardiovascular events (combined fatal or nonfatal MI or sudden death: BIP study primary end point) were estimated with adjustment for all available variables that were considered to be potential confounders and/or predictors of events based on univariable analysis, clinical judgment, and data from the scientific literature. Variables included in the models for BIP study primary end point and new diabetes were age, sex, HOMA-IR, total cholesterol, natural logarithm (ln)–transformed triglycerides, ln-transformed C-reactive protein (CRP), blood pressure, heart rate, history of hypertension, diabetes, previous MI, stroke, heart failure, peripheral vascular disease, anginal syndrome, chronic obstructive pulmonary disease, smoking status, study medication, and body mass index (BMI). A model for new diabetes without BMI was used as well.

A P value of <.05 (2-sided) was considered as statistically significant.

Table I. Baseline characteristics of the study population in accordance with HOMA-IR at baseline

Characteristics	Tertile 1 of HOMA-IR (n = 968)	Tertile 2 of HOMA-IR (n = 1002)	Tertile 3 of HOMA-IR (n = 968)	*P*
Age (y)	59.9 ± 6.7	60.1 ± 6.7	60.4 ± 6.8	.3
BMI (kg/m^2)	25.5 ± 2.7	26.4 ± 2.9	28.2 ± 3.6	<.0001
Men	892 (92)	928 (93)	864 (89)	.02
Diabetes	71 (7)	100 (10)	260 (27)	<.0001
Past MI	764 (79)	769 (77)	759 (79)	.5
Angina	551 (57)	562 (56)	567 (59)	.5
Hypertension	257 (27)	309 (31)	385 (40)	<.0001
Current smokers	125 (13)	105 (11)	116 (12)	.3
Past smokers	528 (55)	623 (62)	580 (60)	.002
Systolic blood pressure (mm Hg)	132 ± 17	133 ± 18	138 ± 18	.0007
Diastolic blood pressure (mm Hg)	80.1 ± 8.9	80.7 ± 9.2	81.9 ± 9.0	<.0001
Glucose (mg/dL)	94 ± 14	98 ± 15	110 ± 19	<.0001
Total cholesterol (mg/dL)	212 ± 18	212 ± 17	213 ± 18	.3
HDL-C (mg/dL)	35.3 ± 5.4	34.5 ± 5.5	33.8 ± 5.5	<.0001
LDL cholesterol (mg/dL)	150 ± 17	148 ± 16	148 ± 17	.03
Triglycerides (mg/dL)	136 ± 49	144 ± 50	156 ± 53	<.0001
CRP (mg/dL)	5.06 ± 5.9	5.48 ± 7.4	6.56 ± 8.1	<.0001
Fibrinogen (mg/dL)	344 ± 71	345 ± 74	357 ± 73	.0005
Insulin (μU/mL)	1.97 ± 1.0	4.6 ± 1.0	9.92 ± 6.5	<.0001
HOMA-IR	0.45 ± 0.2	1.11 ± 0.2	2.7 ± 1.8	<.0001

Data are expressed as mean ± SD or number (percentage) of patients. *LDL*, Low density lipoprotein.

Table II. BIP study outcomes and development of new diabetes in accordance with HOMA-IR tertiles

Tertiles of baseline HOMA-IR	New diabetes	Primary end point*	MI	Cardiac death	Total death
1 (n = 968) HOMA-IR <0.78	91/897 (10.1)	11.2	9.4	4.3	8.6
2 (n = 1002) HOMA-IR 0.78 to <1.49	112/900 (12.4)	14.7	11.2	6.3	10.4
3 (n = 968) HOMA-IR ≥1.49	151/708 (21.3)	17.2	14.4	7.1	11.8
P for trend	<.0001	.0002	.0007	.009	.02

Patients with diabetes on baseline were excluded from the new diabetes analysis. Data are presented as percentage of patients (for BIP study outcomes) or as number of new diabetes/number of patients without diabetes on baseline (percentage).
*The primary end point of the BIP study was fatal or nonfatal MI or sudden death.

Results

Our population was divided into 3 groups in accordance with tertiles of HOMA-IR at baseline: (1) tertile 1, HOMA-IR of <0.78 in 968 patients; (2) tertile 2, HOMA-IR of 0.78 to <1.49 in 1002 patients; (3) tertile 3, HOMA-IR of ≥1.49 in 968 patients.

Baseline data (cross-sectional relationship in accordance with tertiles of HOMA-IR)

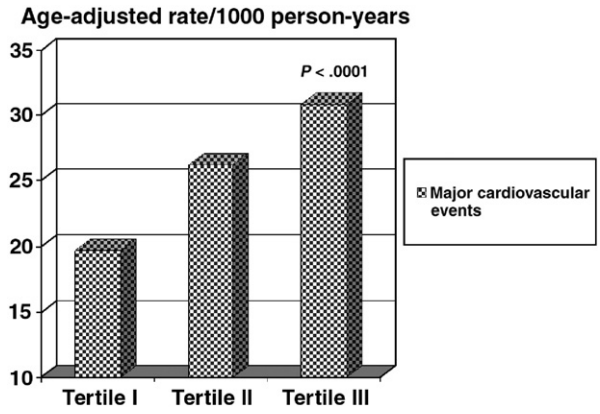
The main clinical and laboratory characteristics of patients are presented in Table I. Most patients in all groups were men. There were no significant differences among the study groups with respect to age, previous MI, and presence of an anginal syndrome. The prevalence of peripheral vascular disease and history of stroke were low in all groups. Among the patients within the top HOMA-IR tertile, a significantly higher proportion had hypertension and diabetes. Body mass index, blood pressure, fasting glucose, insulin, CRP, and triglyceride levels were significantly higher in patients within the top HOMA-IR tertile, whereas HDL-C levels were lower.

β-Blockers, nitrates, calcium antagonists, and antiplatelet drugs (mainly aspirin) were the most commonly used medications in all groups. More patients within the top HOMA-IR tertile, which was frequently associated with diabetes and hypertension, received angiotensin-converting enzyme inhibitors, diuretics, β-blockers, and oral antihyperglycemic drugs (mainly sulfonylureas and metformin) compared with those within the lower tertiles. There were no significant differences in the proportion of patients receiving other cardiovascular drugs.

Clinical outcomes in accordance with HOMA-IR

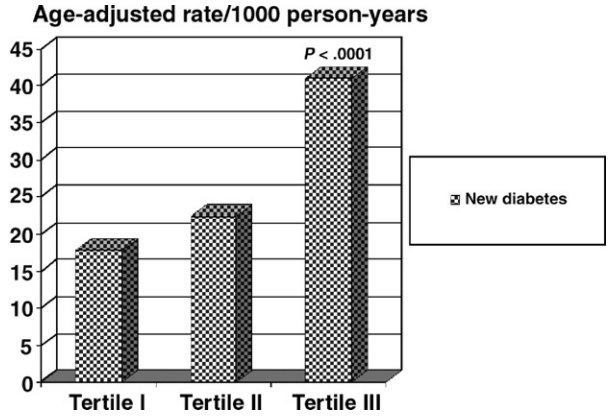
During the follow-up period, development of major cardiovascular events (fatal or nonfatal MI or sudden

Figure 1



BIP study primary end point (major cardiovascular events: combined fatal or nonfatal MI or sudden death) in accordance with tertiles of HOMA-IR at baseline, age-adjusted rate per 1000 person-years.

Figure 2



Development of new diabetes in accordance with tertiles of HOMA-IR at baseline, age-adjusted rate per 1000 person-years.

death: combined BIP study primary end point) was recorded in 421 patients, and new diabetes was recorded in 354 patients (431 patients with diabetes at baseline were excluded from the new diabetes analysis). New major cardiovascular events were recorded in 108 (11.1%) patients from the lowest IR tertile, in 147 (14.7%) from the intermediate tertile, and in 166 (17.2%) from the highest IR tertile (Table II). The linear trend across the tertiles was significant and demonstrated a significantly higher risk for the primary end point (P = .0002), MI (P = .0007), cardiac death (P = .009), total death (P = .02), and development of new diabetes (P < .0001) in the upper tertile of HOMA-IR.

The lowest age-adjusted rate for major cardiovascular events was documented for the group within the bottom HOMA-IR tertile, whereas the highest rate was found among patients within the top tertile of HOMA-IR (57% increased rate, tertile 3 vs tertile 1, P < .0001) (Figure 1). In the subgroup of 2505 patients without diabetes at baseline, the age-adjusted rate for major cardiovascular events was 20.1 per 1000 person-years within the bottom HOMA-IR tertile, 25.2 per 1000 person-years within the intermediate tertile, and 29.4 per 1000 person-years within the top tertile of HOMA-IR (P for trend = .003). An even more pronounced trend was observed for age-adjusted rate of new diabetes (130% increased rate, tertile 3 vs tertile 1, P < .0001) (Figure 2).

Kaplan-Meier curves of incidence of major cardiovascular events (in accordance with the time of diagnosis) for the 3 study groups are presented in Figure 3. The incidence rate of patients within the top HOMA-IR tertile was significantly higher than that of those within the bottom tertile (P log-rank = .001).

Multivariable analysis

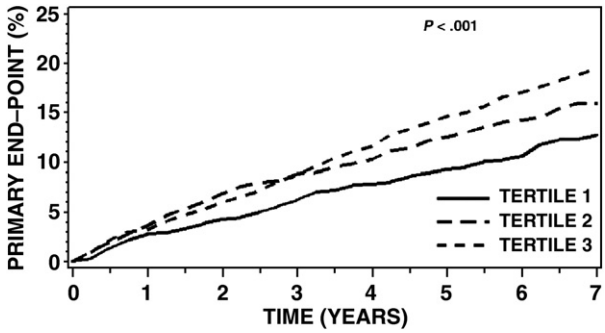
Multivariable analysis with adjustment for potential confounders identified the top HOMA-IR tertile as an independent predictor of increased risk of major cardiovascular events (fatal or nonfatal MI or sudden death) with an HR of 1.4 (95% CI 1.1-1.8, tertile 3 vs tertile 1, P = .01).

Other significant variables associated with future major cardiovascular events were age (10 years increment) with an HR of 1.2 (95% CI 1.03-1.4), male sex with an HR of 1.7 (95% CI 1.1-2.5), previous MI with an HR of 1.5 (95% CI 1.2-2.0), presence of an anginal syndrome with an HR of 1.4 (95% CI 1.1-1.7), chronic obstructive pulmonary disease with an HR of 2.2 (95% CI 1.4-3.3), and CRP with an HR of 1.2 (95% CI 1.1-1.3) per 1 unit of ln increment. Intermediate HOMA-IR tertile was associated with borderline increased risk of major cardiovascular events with an HR of 1.27 (95% CI 0.98-1.6, tertile 2 vs tertile 1, P = .07).

As a continuous variable, HOMA-IR at baseline was independently associated with future major cardiovascular events in multivariable analysis with an HR of 1.13 (95% CI 1.01-1.27) and with new diabetes with an HR of 1.23 (95% CI 1.07-1.41) per 1 unit of ln increment.

In the subgroup of 2505 patients without diabetes at baseline, the top HOMA-IR tertile was also an independent predictor of increased risk of major cardiovascular events with an HR of 1.38 (95% CI 1.04-1.82, tertile 3 vs tertile 1, P = .03). Intermediate HOMA-IR tertile in this subgroup was associated only with a trend to increased risk, which did not reach statistical significance, with an HR of 1.25 (95% CI 0.95-1.65, tertile 2 vs tertile 1, P = .12). In addition, the top tertile of HOMA-IR after multivariable adjustment was strongly associated with the development of new diabetes with

Figure 3



Kaplan-Meier curves of BIP study primary end point incidence (fatal or nonfatal MI or sudden death, 6.2 years mean follow-up, *P* log-rank = .001) for the 3 study groups.

an HR of 1.9 (95% CI 1.6-2.7) in a model excluding BMI and an HR of 1.5 (95% CI 1.1-2.0, $P = .003$) in a model including BMI.

Discussion

This study demonstrates the independent association of HOMA-IR with major cardiovascular events and mortality in a large population of patients with preexisting CAD. Age-adjusted rate for major cardiovascular events was increased by 57% in patients within the top versus those within the bottom HOMA-IR tertile. After multivariable adjustments, the relative hazard of the top HOMA-IR tertile was somewhat attenuated (40% excess risk) but remained significant ($P = .01$). Among studied metabolic and inflammatory parameters, only CRP level, in addition to HOMA-IR, remained significantly associated with major cardiovascular events in a multivariable analysis. This indicates that HOMA-IR and CRP measured in patients with preexisting CAD could independently predict long-term cardiovascular outcome and mortality. Our data corresponded well with the previous study of Yanase et al,[21] which was performed among 102 patients with CAD. In this 3-year observational study, fasting hyperinsulinemia and IR significantly increased the risk of new cardiovascular events in patients with normal glucose tolerance.

In addition, we have examined the cross-sectional relationship between IR and main clinical conditions and metabolic parameters. Preexisting hypertension and diabetes as well as BMI, blood pressure, CRP level, and triglyceride level were considerably higher in patients within the top HOMA-IR tertile, whereas HDL-C level was lower. Our cross-sectional results demonstrated a significant clustering effect of HOMA-IR tertiles presented by the grouping of these recognized cardiovascular risk factors.

We found that HOMA-IR was associated with >2-fold increased age-adjusted risk for the development of diabetes in nondiabetic subjects. After adjustment for multiple potential confounders, the prediction conferred by the top HOMA-IR tertile for new diabetes was substantially attenuated, mainly after inclusion of BMI in the model, yet remained strongly significant (50% excess risk, $P = .003$). Consequently, IR and BMI are most likely associated with diabetes development by partially (but not completely) mutual mechanisms. Therefore, IR per se is an independent risk factor for cardiovascular events and new diabetes in patients with preexisting CAD. In this regard, our data extend previous observations[1-3,22] by examining the specific high-risk population of patients with preexisting CAD.

Development of IR has been considered to be important in the progression of the metabolic syndrome, diabetes, and probably CAD, where its effect is partially mediated by traditional cardiovascular risk factors.[23-25] Moreover, IR probably has several pleiotropic effects, including dyslipidemia, direct promotion of atherogenesis, hypertension, inflammation, and endothelial dysfunction.[26-29] It represents a complex interaction of maladaptive characteristics related to impaired insulin action at target organs and external factors such as genetics and environment. It is likely that the molecular factors that underlie IR (mediated in part via nuclear peroxisome proliferator–activated receptors) contribute to many of the clinical components of the metabolic syndrome and CAD, although the precise associations remain poorly understood.[25-29]

A number of major clinical trials have demonstrated the beneficial effects of peroxisome proliferator–activated receptors agonists (fibrates and glitazones) on cardiovascular disease outcomes.[30-34] One common link among these trials was a cohort with a high prevalence of metabolic syndrome or diabetes, conditions associated with IR, and increased risk for development and progression of atherosclerosis.

Methods to assess insulin sensitivity and secretion directly (mainly the hyperinsulinemic euglycemic glucose clamp technique) are complicated and are not easily implemented in large studies.[35] Homeostasis model assessment of IR has been suggested as a method to assess IR from the fasting glucose and insulin concentrations and provides a useful model to assess IR in epidemiological studies and clinical trials.[36-38] In this study, we have shown that HOMA-IR is a valid predictor of the major cardiovascular events, development of diabetes, and mortality. Homeostasis model assessment of IR may provide a simple, practical, and inexpensive method for identifying insulin-resistant individuals and probably should be considered in the risk stratification of patients with preexisting CAD within secondary prevention framework. Furthermore, clinically detected increased IR may be a stimulus for more aggressive

therapeutic approach and appropriate intensive lifestyle changes in these high-risk patients, whereas HOMA-IR itself may be a target for future treatment interventions. This is of potential clinical importance, given the current availability of therapies that directly and indirectly reduce IR.[39–42] Obviously, further investigations regarding the validity of such approach on patient outcomes are required.

Study limitations

Our study has several important limitations. Among diabetic patients, fasting insulin levels could be affected differently by the oral antidiabetic agents. Moreover, different cardiovascular event rates could have been associated with the different agents (eg, metformin vs sulfonylurea). To partially answer these questions, we present a subgroup analysis of 2505 patients without diabetes on baseline (431 diabetic patients were excluded): the top HOMA-IR tertile was also an independent predictor of about 40% increased risk of major cardiovascular events in these patients.

An additional limitation in our study was the strong male predominance (>90%) among the trial population. Therefore, all results should be interpreted within this limitation.

Conclusions

Insulin resistance per se calculated by homeostasis model assessment is an independent risk factor for major cardiovascular events (fatal or nonfatal MI or sudden death) and new diabetes in patients with preexisting CAD.

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