



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

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Abstract

Objective: This study aims to investigate whether homeostasis model assessment-estimated insulin resistance (HOMA-IR) serves as an independent predictor of cardiovascular disease (CVD) in individuals with type 2 diabetes.

Methods: We conducted a longitudinal study involving 1,326 patients diagnosed with type 2 diabetes. At baseline and after an average follow-up period of 4.5 years, we assessed conventional CVD risk factors (such as sex, age, smoking, plasma lipids, blood pressure, and metabolic control) and insulin resistance estimated by HOMA-IR. CVD was evaluated through medical history, physical examination, electrocardiography, and echo-Doppler of carotid and lower limb arteries. Cardiovascular deaths were identified by reviewing death certificates and medical records.

Results: Among the participants, 441 were identified with prevalent CVD at baseline, while 126 developed incident CVD during the follow-up period. Multiple logistic regression analyses revealed that, in addition to established CVD risk factors, HOMA-IR independently predicted both prevalent and incident CVD. A one-unit increase in (log)HOMA-IR 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: Our findings indicate that HOMA-IR serves as an independent predictor of CVD in individuals with type 2 diabetes. Addressing insulin resistance may not only improve glucose control but also potentially mitigate the risk of CVD in this patient population.

Introduction:

Diabetes contributes significantly to accelerated atherosclerosis, with type 2 diabetic individuals facing a fivefold higher risk of advanced atherosclerosis compared to nondiabetic individuals, even after adjusting for various confounders. This heightened risk translates into several-fold increases in coronary heart disease (CHD), cerebrovascular disease, and peripheral vascular disease among those with type 2 diabetes, making cardiovascular diseases (CVDs) the primary cause of mortality in this population. (Bonora et al., 2000)

While type 2 diabetes involves multiple abnormalities related to atherosclerosis risk factors such as plasma lipids, blood pressure, and the coagulation cascade, these classic risk factors only account for about a quarter of the increased cardiovascular risk seen in type 2 diabetes. The role of hyperglycemia in contributing independently to this risk has been noted, although it remains a topic of debate. Another potential contributor is insulin resistance, prevalent in the majority of type 2 diabetes cases. (De Marco et al., 1999) Numerous cross-sectional studies have demonstrated an independent association between insulin resistance and subclinical or clinical CVD in both diabetic and nondiabetic populations. However, robust evidence

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supporting a causal link between insulin resistance and CVD requires longitudinal studies and intervention trials, which have been relatively scarce. Currently, there exists only one comprehensive study and a few abstracts based on longitudinal data exploring the relationship between insulin resistance and CVD. (Bonora et al., 1998)

This study aims to contribute to this growing body of evidence by investigating the association between insulin resistance, as estimated using the homeostasis model assessment (HOMA), and CVD (Haffner et al., 1997)

Research Design and Methods:

Subjects:

Study is a longitudinal cohort study to identify risk factors of chronic complications in type 2 diabetes. The baseline evaluation included 1,780 subjects randomly recruited among a total of approximately 25,000 patients regularly attending the Diabetes Clinics and surrounding areas. Patients with major comorbidities and intercurrent illnesses were excluded, with one to two patients included in the study each day. Of the 2,000 patients invited to participate, the response rate was 89%.

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 provided informed consent to participate in the study, which had been approved by the local Ethical Committee.

Clinical Data:

At baseline, demographic and clinical data were collected using a standardized questionnaire, including sex, age, cigarette smoking, physical activity at work and leisure, socioeconomic status, previous diseases, and drug consumption. Information on cigarette smoking included smoking status, average daily cigarette consumption, and years of smoking. Physical activity levels were categorized for work and leisure time. Body weight, height, BMI, waist and hip circumferences, and waist-to-hip ratio (WHR) were measured. Blood pressure was recorded using standard methods, and hypertension was diagnosed according to established criteria.

Laboratory Data:

Venous blood samples were collected at baseline after an overnight fast for measuring HbA1c, plasma glucose, total and HDL cholesterol, triglycerides, and insulin levels. Plasma glucose was measured using a glucose-oxidase method, HbA1c by high-performance liquid chromatography, and lipids by enzymatic spectrophotometric techniques. Insulin levels were assessed using radioimmunoassay.

Assessment of Insulin Resistance:

Insulin resistance was estimated at baseline using the homeostasis model assessment (HOMA) method described by Matthews et al. (19). The HOMA-IR score was calculated using fasting plasma glucose and serum insulin levels.

Assessment of Cardiovascular Disease (CVD):

CVD was assessed at baseline and follow-up through medical history, physical examination, echo-Doppler examination of carotid and lower limb arteries, and 12-lead electrocardiography (ECG). The presence of CHD, cerebrovascular disease, peripheral vascular disease, and other CVD-related conditions was documented.

Statistical Analyses:

Statistical analyses were performed using SPSS software and multiple logistic regression analyses. Various models were tested, including different explanatory variables such as demographic data, clinical parameters, and laboratory measurements. Data were presented as means $\pm$ SE.

Results:

The main clinical and biochemical features of the cohort are summarized in Table 1. Men and women were equally represented, with an average age of 64 years and a mean diabetes duration of approximately 9 years.

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Most subjects were overweight or obese and had dyslipidemia and/or hypertension. Metabolic control was mostly good or fair, and the majority of patients were treated with oral agents.

At baseline, (log)HOMA-IR showed significant correlations with various factors such as age, duration of diabetes, BMI, WHR, (log)HDL cholesterol, (log)triglycerides, diastolic blood pressure, fasting glucose, HbA1c, and (log)fasting insulin. These correlations remained significant in multivariate analyses accounting for sex, age, and BMI.

At baseline, 33% of subjects were coded positive for CVD, with 11% positive for CHD. At follow-up, 46% of subjects had prevalent CVD, including CHD, cerebrovascular disease, and peripheral vascular disease. Incident CVD cases during follow-up were recorded in 20% of patients who were initially free of CVD.

Sex, age, smoking, total/HDL cholesterol ratio, hypertension, and (log)HOMA-IR were independent predictors of prevalent CVD at baseline. Age, smoking, total/HDL cholesterol ratio, and HOMA-IR were independently associated with incident CVD during follow-up. (log)HOMA-IR was particularly notable, with each unit increase associated with a 31% increase in baseline CVD risk and a 56% increase in incident CVD risk.

Further analyses showed that (log)HOMA-IR remained a predictor of prevalent CVD across different BMI, HbA1c, and diabetes duration categories. However, its significance as a predictor of incident CVD varied based on these categories.

When (log)fasting insulin replaced (log)HOMA-IR in the models, it was significantly associated with prevalent CVD but not incident CVD during follow-up.

The results were consistent across various model configurations, highlighting the independent predictive value of (log)HOMA-IR for CVD in type 2 diabetes.

Discussion:

Insulin resistance plays a significant role in type 2 diabetes and is associated with various cardiovascular risk factors. This study aimed to determine whether insulin resistance contributes to atherosclerosis and cardiovascular disease (CVD) independently of other risk factors. (Bonora et al., 1998)

The findings indicate that insulin resistance, as assessed by HOMA, is a strong predictor of both prevalent CVD at baseline and incident CVD during follow-up in type 2 diabetic patients. This predictive value was observed even after accounting for classic risk factors and variables closely related to insulin resistance, such as BMI. (Bonora et al., 2000)

The study underscores the importance of targeting insulin resistance in the management of type 2 diabetes, not only for controlling hyperglycemia but also for reducing CVD risk. Therapeutic interventions that improve insulin sensitivity, such as physical activity and certain medications like metformin and troglitazone, have shown benefits in preventing CVD events. (Bonora et al., 2001)

While the study did not use the gold standard glucose clamp for assessing insulin sensitivity, HOMA has been shown to be a reliable tool in both diabetic and nondiabetic subjects. The study's results align with previous cross-sectional and longitudinal studies, highlighting the consistent association between insulin resistance and CVD risk. (Hu et al., 2001)

The mechanisms linking insulin resistance to atherosclerosis and CVD are complex and involve various pathways such as platelet function, endothelial function, smooth muscle cell migration, and fibrinogen synthesis. Insulin's potentially antiatherogenic properties may be impaired in insulin-resistant states, contributing to increased atherosclerosis. (Targher et al., 1997)

Overall, the study suggests that addressing insulin resistance could be a crucial aspect of CVD prevention in type 2 diabetes. Future trials focusing on the impact of insulin-sensitizing therapies on CVD incidence in diabetic patients are eagerly anticipated. (Howard et al., 1996)

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