Available online at www.sciencedirect.com
ScienceDirect
Diabetes Research and Clinical Practice 74 (2006) 316–321
DIABETES RESEARCH AND CLINICAL PRACTICE
www.elsevier.com/locate/diabres

Coexistence of insulin resistance and inflammation effectively predicts cardiac disease but not stroke in Japanese patients with type 2 diabetes mellitus

Kazunari Matsumoto [a,*], Naruhiro Fujita [a], Masako Ozaki [a], Tan Tominaga [b], Yukitaka Ueki [b], Seibei Miyake [a]

[a] *Diabetes Center, Sasebo Chuo Hospital, 15 Yamato-cho, Sasebo, Nagasaki 857-1195, Japan*
[b] *Department of Internal Medicine, Sasebo Chuo Hospital, 15 Yamato-cho, Sasebo, Nagasaki 857-1195, Japan*

Received 24 February 2005; received in revised form 22 March 2006; accepted 7 April 2006
Available online 30 May 2006

Abstract

It is well known that insulin resistance (IR) and inflammation (IF) are associated with macroangiopathy. However, whether IR and IF are related to cardiac disease (myocardial infarction, angina pectoris, and heart failure), stroke or both remains elusive. The present hospital-based prospective study was designed to investigate this issue. The study subjects were 300 Japanese patients with type 2 diabetes mellitus and negative history of cardiac disease and stroke. IR (*K* index of insulin tolerance test; K_{ITT}) and IF (high-sensitivity C-reactive protein [hs-CRP]) were measured in each patient at baseline. Patients were followed-up for a mean period of 5.5 years. The time of first evidenced cardiac disease or stroke was monitored. During the follow-up, 35 patients developed cardiac disease and 26 patients developed stroke. Age, smoking, K_{ITT}, and hs-CRP were independently related to cardiac disease, while age, systolic blood pressure, low HDL, and anti-platelet drug use were independently related to stroke. When patients were subdivided into IR(−) and IR(+), and IF(−) and IF(+), Kaplan-Meier survival analysis showed that the rate of cardiac disease, but not of stroke, was significantly higher in IR(+)IF(+) than IR(−)IF(−) patients ($p < 0.01$). In conclusion, coexistence of IR and IF effectively predicted cardiac disease but not stroke in Japanese patients with type 2 diabetes mellitus.

Keywords: Insulin resistance; C-reactive protein; Cardiac disease; Stroke; Type 2 diabetes mellitus

1. Introduction

Patients with type 2 diabetes mellitus are at high risk of atherosclerotic vascular disease. It is well known that insulin resistance (IR) and low-grade inflammation (IF) are closely related to atherosclerosis [1–3]. Recently, we reported that both IR and IF are independently related to all-cause of death and cardiovascular disease including coronary heart disease, heart failure, and stroke in Japanese patients with type 2 diabetes [4]. However, we did not demonstrate the effects of IR and IF on each of cardiac disease and/or stroke [4]. It is not known whether these markers are related to cardiac disease (coronary heart disease and heart failure) or stroke, or both. If any relationship is present, it is useful to identify the patients with high risk at cardiac disease or stroke. Japanese patients with type 2 diabetes have lower incidence of cardiac disease compared with Caucasians [5]. The incidences of cardiac disease and

* Corresponding author. Tel.: +81 956 33 7151; fax: +81 956 34 3241.
E-mail address: dmkmatsu@hakujyujikai.or.jp (K. Matsumoto).

0168-8227/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.diabres.2006.04.014

stroke in patients with type 2 diabetes are almost similar in Japan [5]. Thus, a comparable number of patients develop cardiac disease and stroke. Therefore, the separation of risk factors related to cardiac disease and stroke is an important issue. For that reason, we further analyzed our hospital-based data [4] with the aim of defining the differences between cardiac disease and stroke in relation to IR and IF in patients with type 2 diabetes mellitus.

2. Patients and methods

This study is a sub-analysis of our previous study published elsewhere [4]. The patients in this study were almost the same of those included in our previous report [4]. A total of 350 Japanese patients with type 2 diabetes were recruited in the original study [4]. We excluded from that group all patients who had a positive history of cardiac disease or stroke at entry ($n = 40$). We also excluded those patients who died due to non-cardiovascular diseases (e.g. cancer, $n = 10$). Thus, the present study was conducted in 300 patients who had no macrovascular complications at entry. These patients had no heart failure (NYHA grade $\geq$2), renal failure (serum creatinine $>$2.0 mg/dl), liver disease, endocrine disease, or intercurrent infection as described previously [4].

At baseline, insulin sensitivity and high-sensitivity C-reactive protein (hs-CRP) were measured in all patients. It is well known that hyperglycemia per se can induce IR known as glucose toxicity. To minimize the effect of glucose toxicity, patients were admitted to Sasebo Chuo Hospital and treated with either diet, oral hypoglycemic agents or insulin before the measurement of insulin sensitivity and hs-CRP. The target level was below 7.8 mmol/l for fasting glucose and below 11.1 mmol/l for post-prandial glucose.

Insulin sensitivity was measured by the K index of short insulin tolerance test (K_{ITT}), which had been validated by Bonora et al. [6]. On the day of examination, oral hypoglycemic agents and insulin were withheld. An insulin tolerance test was carried out after an overnight fast of 12–14 h. K_{ITT} represents the rate of disappearance of glucose in insulin tolerance test. Briefly, a bolus of regular insulin (0.1 U/kg) was infused and blood samples were collected at 3, 6, 9, 12, and 15 min after infusion [7]. K_{ITT} was calculated using the formula $K_{ITT} = 0.693/t_{1/2}$. Baseline serum samples were stored at -60 °C. We measured hs-CRP level in the stored serum using an automated high-sensitivity method (Dade Behring, Tokyo, Japan). The reference cut-off level in Japan for hs-CRP is $\leq$0.09 mg/dl (Dade Behring). We also measured fasting plasma glucose, HbA1c, total cholesterol, triglyceride, and HDL cholesterol levels using standard procedures. We followed these patients for 2–8 years (mean follow-up period; 5.5 years).

The endpoint of the present study was first event of fatal and non-fatal cardiac disease or stroke. Cardiac disease was diagnosed based on the (1) development of acute myocardial infarction, (2) angina pectoris confirmed by coronary angiography, or (3) heart failure that required hospitalization regardless the cause. Stroke was diagnosed based on typical neurological deficit and confirmed by computed tomography or magnetic resonance imaging. Cerebral bleeding was also included as event.

Informed consent was obtained from each patient. The study protocol was approved by the ethics committee of Sasebo Chuo Hospital. Unpaired data were analyzed by Student's t-test or contingency table analysis. Multiple comparisons were performed by ANOVA with post hoc test. Relative risk was estimated by Cox's proportional hazard model. The negative values of K_{ITT} (zero-K_{ITT}) and HDL cholesterol (zero-HDL cholesterol) were used because these variables correlated inversely with cardiovascular disease. The values of hs-CRP were used after log transformation because of their skewed deviation. Kaplan-Meier analysis was used to estimate the survival curve using log-rank test to determine the difference in duration of occurring event within patients with IR and/or IF. In this analysis, patients were subdivided into IR(+) and IR(−) using a K_{ITT} cut-off level of 2.50%/min [patients with K_{ITT} value $<$2.50%/min were IR(+)]. This cut-off value was selected based on the results of our previous studies [8–10]. Specifically, about 45% of the examined Japanese diabetic patients were insulin resistant [9], and the 45‰ value of K_{ITT} in diabetes was 2.50%/min. We also subdivided the patients into IF(+) and IF(−) according to the hs-CRP level [IF(+) represented those with hs-CRP value $>$0.10 mg/dl]. This cut-off value was selected by three reasons. First, referenced cut-off level of the commercial kit is hs-CRP $\leq$0.09 mg/dl (Dade Behring). Second, American Heart Association reported that hs-CRP $\geq$1 mg/l showed an average risk. Third, we previously reported that hs-CRP $\geq$0.11 mg/dl showed high risk for all-cause of death and cardiovascular disease [4]. Differences were considered statistically significant at $p < 0.05$. Statistical analysis was performed using Statview 5.0J software package (SAS, Cary, NC).

3. Results

During the 5.5-year follow-up period, 35 patients developed cardiac disease (including eight cases of heart failure) and 26 patients developed stroke. Only one patient developed both cardiac disease and stroke. The baseline characteristics of patients who did or did not develop cardiac disease are listed in Table 1. Patients who developed cardiac disease were significantly older and had longer duration of diabetes, and higher percentages of these patients were smokers and on insulin treatment, and their HDL cholesterol levels were lower, IR was higher (lower K_{ITT}), and hs-CRP levels were higher, compared with those free of cardiac event (Table 1). To select the independent factors related to cardiac disease, we performed multivariate Cox's proportional hazard model and calculated the