Systematic Analysis of Risk Factors for Coronary Heart Disease in Japanese Patients with Type 2 Diabetes: A Matched Case-Control Study

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Aim: To identify predictors of coronary heart disease (CHD) in Japanese patients with type 2 diabetes (T2DM).

Methods: A matched case-control study was performed using 800 patients with T2DM admitted for treatment of hyperglycemia from January 2002 to June 2010. Cases comprised 16 patients who had developed acute myocardial infarction and/or received a coronary artery bypass by June 2010, and controls comprised 48 age- and sex-matched patients without CHD events. The mean age, glycated hemoglobin (HbA1c), and body mass index (BMI) were 61.5 yrs, 9.7% and 24.4 kg/m², respectively. The relationship of baseline variables, including lipid values, HbA1c, BMI, blood pressure, fasting blood sugar, 2h-post-breakfast blood sugar, delta blood sugar0-2h, urinary albumin excretion, estimated glomerular filtration rate and treatment modalities (insulin/sulfonylurea/biguanide), to CHD development was analyzed by conditional logistic regression analysis.

Results: Total cholesterol (TC) (OR 2.35, 95%CI 1.11-4.98, \(p=0.03\)), non-HDL-cholesterol (OR 3.07, 95%CI 1.33-7.10, \(p=0.009\)), LDL-cholesterol (OR 2.84, 95%CI 1.24-6.51, \(p=0.01\)), non-HDL-cholesterol/HDL-cholesterol (OR 2.07, 95%CI 1.10-3.90, \(p=0.02\)) and LDL-cholesterol/HDL-cholesterol (OR 2.74, 95%CI 1.22-6.15, \(p=0.01\)) were significantly related to CHD. Fold risk increment per 1-SD increase in basal TC, non-HDL-cholesterol, LDL-cholesterol, non-HDL-cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol was 2.33, 2.89, 2.52, 2.37 and 2.60, respectively. Only non-HDL-cholesterol was an independent risk factor. From the receiver operating characteristic curve, 3.89 mmol/L non-HDL-C was the best cutoff value. None of the non-lipid variables were significantly related to CHD.

Conclusion: Non-HDL-cholesterol was the most dominant predictor of the development of CHD in Japanese patients with T2DM.


Key words: Coronary heart disease, Lipid parameter, Non-HDL-cholesterol, Diabetes

Introduction

Coronary heart disease (CHD) is the leading cause of death in type 2 diabetes mellitus (T2DM)¹, and its prediction, prevention and treatment are very important. There are many risk factors for the development of CHD in diabetes. In addition to hyperglycemia per se, dyslipidemia and hypertension play major roles². Recently, the possible deleterious effect of postprandial hyperglycemia on CHD has been proposed³. Furthermore, microalbuminuria, a marker of early phase diabetic nephropathy, is also a predictor of
development of CHD. Regarding lipid parameters, the usefulness of non-HDL-cholesterol (non-HDL-C) to HDL-C ratio as a predictor of cardiovascular risk in patients with T2DM has been reported in Caucasian patients. Thus, the legitimacy of current guidelines emphasizing LDL cholesterol (LDL-C) as the primary treatment target for CHD risk prediction was questioned. Here we systematically investigated the relationship of known risk factors for the development of CHD in Japanese patients with T2DM. The aim of the study was to identify the most dominant risk factor for the development of CHD. More specifically, we tried to elucidate the relative predictive power of lipid and non-lipid risk factors for CHD in everyday clinical practice with Japanese patients with T2DM.

Methods

The study was approved by Aizawa Hospital Review Board. A matched case-control study was performed using 800 consecutive patients with T2DM admitted to Aizawa Hospital Diabetes Center for the control of hyperglycemia from January 2002 to June 2010 without having a history of CHD. Aizawa Hospital has an electronic patient records system that can be used retrospectively to evaluate selected patients. Charts of the 800 patients were screened for re-admission for treatment of acute myocardial infarction (AMI) and/or a coronary artery bypass graft (CABG). The screening period was from January 2002 to June 2010. Sixteen patients were identified by screening and were adopted as CHD cases. The mean (±SD, range) period between the initial admission for treatment of hyperglycemia and admission for treatment of CHD was 2.1 (±2.0, 0.1-6.6) yrs. From the same 800 patients, 48 age- and sex-matched patients who had not developed CHD were selected as controls (3 controls for each CHD case). The selection was performed without knowing the laboratory and anthropometric data of each patient. Three controls for 2 CHD cases, 1 for each CHD case, respectively, were quasi-age-matched (1 yr older and younger). This was because the required number, i.e., three, of age-matched controls did not exist for the 2 patients with CHD.

As shown in Table 1, total cholesterol (TC), HDL-C, triglycerides (TG), non-HDL-C, LDL-C, TC/HDL-C, non-HDL-C/HDL-C, TG/HDL-C, LDL/C/HDL-C were adopted as the baseline lipid variables. As non-lipid variables, the body mass index (BMI), glycosylated hemoglobin (Hba1c), fasting blood sugar (FBS), 2h-post-breakfast BS, difference between FBS and 2hBS (δBS0-2h), urinary albumin excretion (UAE), estimated glomerular filtration rate (eGFR) and blood pressure were used. The treatment modality, i.e., insulin, sulfonylurea or biguanide, was also incorporated into the analysis as a baseline variable. The status of the use of antihypertensive drugs was not analyzed.

Blood sampling for lipids and creatinine was performed before breakfast after an overnight fast. Hba1c was determined by HPLC (HA-8170; Arkray). LDL-C was directly determined by an enzymatic method with reagents obtained from Sekisui Medical. LDL-C calculated by Friedewald formula (cLDL-C) was also utilized for analysis. TG was <4.0 mmol/L in all 64 subjects analyzed in this study. Japan Diabetes Society Hba1c was converted to NGSP values. BS was determined by Glutest and eGFR was calculated by the formula developed for Japanese subjects.

By conditional logistic regression analysis, the relationship of the baseline variables to the development of CHD was investigated. Statistical analysis was performed using SPSS ver. 19.0 and p < 0.05 was considered significant. Knowing that elevated non-HDL-C was the only variable independently related to CHD, the best cutoff value of non-HDL-C for predicting CHD was obtained from the receiver operating characteristic (ROC) curve.

Results

The mean (±SD) age and BMI of all 800 patients were 58.9 ± 11.9 yrs and 24.9 ± 4.4 kg/m², respectively, and the male/female ratio was 514/286. Characteristics of the patients used for the current study are shown in Table 1. The male/female ratio was 56/8, and the mean age, BMI, Hba1c, FBS, UAE and systolic blood pressure were 61.5 yrs, 24.4 kg/m², 9.7%, 8.7 mmol/L, 301 mg/day and 131 mmHg, respectively. The mean values of TC, non-HDL-C, LDL-C, non-HDL-C/HDL-C (TC/HDL-C) and LDL-C/HDL-C were significantly higher in Cases than in Controls (Table 1). Cases and Controls were not significantly different regarding other variables, including the prevalence of statin use (Table 1).

By univariate conditional logistic regression analysis, TC (OR 2.35, 95%CI 1.11-4.98, p = 0.03), non-HDL-C (OR 3.07, 95%CI 1.33-7.10, p = 0.009), LDL-C (OR 2.84, 95%CI 1.24-6.51, p = 0.01), non-HDL-C/HDL-C (TC/HDL-C) (OR 2.07, 95%CI 1.33-3.09, p = 0.02) and LDL-C/HDL-C (OR 2.74, 95%CI 1.22-6.15, p = 0.01) were significantly related to the development of CHD (Table 2). Relation of cLDL-C (OR 2.96, 95%CI 1.25-7.05, p = 0.01) and cLDL-C/HDL-C (OR 2.57, 95%CI 1.80-5.59, p = 0.02) to CHD was similar to the relationship of LDL-C and LDL-C/HDL-C to CHD, respectively.
The odds ratio per 1-SD increase in basal TC, non-HDL-C, LDL-C, non-HDL-C/HDL-C (TC/HDL-C) and LDL-C/HDL-C was 2.33, 2.89, 2.52, 2.37 and 2.60, respectively. None of the non-lipid variables was significantly related to the development of CHD (Table 2), and neither was the treatment modality.

Variables showing a significant association with the development of CHD in univariate analysis were entered into stepwise conditional multiple logistic regression analysis, in which only non-HDL-C was independently related to CHD.

When the participants were grouped on the basis of quartiles of baseline non-HDL-C, development of CHD was progressively more frequent with higher non-HDL-C (Fig.1). The ROC curve revealed that the basal non-HDL-C of 3.89 mmol/L was the optimal cutoff value to segregate patients who had developed CHD with 75% sensitivity and 60% specificity (Fig. 2).

### Discussion

Atherosclerosis is a multi-factorial disorder so comprehensive analysis of the risk factors has been proposed. This is especially true in patients with diabetes so we systematically compared the effects of the mean glycemia (HbA1c), postprandial glycemia, early phase nephropathy as indexed by UAE and eGFR, blood pressure, and a series of lipid parameters on the development of CHD in this study. As far as we are aware, no study has been performed previously that incorporated as many risk factors as this study.

Firstly, lipid parameters were unequivocally related to the development of CHD, whereas none of the non-lipid variables was significantly related. This finding suggested the primacy of dyslipidemia as a causal factor for CHD. The deleterious effect of dyslipidemia on atherosclerosis in patients with diabetes
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The difference might be due to the male dominance in the current cohort: serum HDL-C concentration is generally lower in males than in females. Increased TG and LDL-C were identified as independent risk factors for the development of CHD in Japanese patients with T2DM with a mild degree of hyperglycemia. Nevertheless, the effect of non-HDL-C on CHD risk was not evaluated in this study. The importance of non-HDL-C as a cardiovascular risk was also found in a recent study of a dyslipidemic population and Japanese general populations. Thus, the superiority of non-HDL-C over LDL-C as a CHD risk may be a common phenomenon beyond ethnic, anthropometric and metabolic diversities. Elevated non-HDL-C has been considered a predictor of the development of CHD because the amount of circulating atherogenic lipid particles can be more faithfully reflected in serum non-HDL-C than LDL values, especially in patients with diabetes. In other words, elevation of non-HDL-C is most likely causal for, rather than a simple marker of, CHD. In a community-based study, an optimal non-HDL-C cutoff value of 3.63 mmol/L for the prediction of CHD risk in this study. The difference might be due to the male dominance in the current cohort: serum HDL-C concentration is generally lower in males than in females. Increased TG and LDL-C were identified as independent risk factors for the development of CHD in Japanese patients with T2DM with a mild degree of hyperglycemia. Nevertheless, the effect of non-HDL-C on CHD risk was not evaluated in this study. The importance of non-HDL-C as a cardiovascular risk was also found in a recent study of a dyslipidemic population and Japanese general populations. Thus, the superiority of non-HDL-C over LDL-C as a CHD risk may be a common phenomenon beyond ethnic, anthropometric and metabolic diversities. Elevated non-HDL-C has been considered a predictor of the development of CHD because the amount of circulating atherogenic lipid particles can be more faithfully reflected in serum non-HDL-C than LDL values, especially in patients with diabetes. In other words, elevation of non-HDL-C is most likely causal for, rather than a simple marker of, CHD. In a community-based study, an optimal non-HDL-C cutoff value of 3.63 mmol/L for the prediction of

| Table 2. Results of univariate logistic regression analysis |
|-----------------|-----------------|-----------|-----------------|-----------|
| Variable        | OR per 1-unit increase | 95%CI for OR per 1-unit increase | \( p \)     | OR per 1-SD increase | 95%CI for OR per 1-SD increase |
| Lipid parameters |                 |           |                 |           |
| TC, mmol/L      | 2.35            | 1.11-4.98 | 0.03            | 2.33      | 1.12-4.85  |
| HDL-C, mmol/L   | 0.40            | 0.05-3.19 | 0.38            | N.A.      |            |
| TG, mmol/L      | 2.09            | 0.63-6.88 | 0.23            | N.A.      |            |
| NonHDL-C, mmol/L| 3.07            | 1.33-7.10 | 0.009           | 2.89      | 1.33-6.31  |
| LDL-C, mmol/L   | 2.84            | 1.24-6.51 | 0.01            | 2.52      | 1.22-5.20  |
| TC/HDL-C        | 2.07            | 1.10-3.90 | 0.02            | 2.37      | 1.15-4.89  |
| NonHDL-C/HDL-C  | 2.07            | 1.10-3.90 | 0.02            | 2.37      | 1.15-4.89  |
| TG/HDL-C        | 1.92            | 0.70-5.25 | 0.20            | N.A.      |            |
| LDL-C/HDL-C     | 2.74            | 1.22-6.15 | 0.01            | 2.60      | 1.24-5.45  |
| Non-lipid variables |           |           |                 |           |
| BMI, kg/m²      | 1.05            | 0.86-1.28 | 0.65            | N.A.      |            |
| NGSP-Hba1c, %   | 1.19            | 0.85-1.68 | 0.32            | N.A.      |            |
| FBS, mmol/L     | 1.15            | 0.84-1.59 | 0.38            | N.A.      |            |
| 2hBS, mmol/L    | 1.12            | 0.93-1.34 | 0.24            | N.A.      |            |
| δBS2-2h, mmol/L | 1.10            | 0.89-1.36 | 0.39            | N.A.      |            |
| UAE, mg/day     | 1.00            | 0.99-1.00 | 0.40            | N.A.      |            |
| eGFR, mL/min/1.73 m² | 0.99          | 0.96-1.02 | 0.52            | N.A.      |            |
| SBP, mmHg       | 0.99            | 0.95-1.03 | 0.56            | N.A.      |            |
| DBP, mmHg       | 0.97            | 0.89-1.06 | 0.51            | N.A.      |            |

OR, odds ratio; CI, confidence interval; SD, standard deviation; OR per 1-SD increase and the respective 95%CI were obtained for variables significantly related to CHD. N.A., not applicable. See Table 1 for other abbreviations. See text for details.
CHD was proposed\cite{24}, which was slightly lower than the corresponding value found in this study.

Lastly, the number of patients evaluated in this study was small and this was a single center analysis. Also, we analyzed the relationship of clinical variables and severe CHD alone, i.e., relationship of the variables to mild CHD such as angina pectoris was not analyzed. In addition, information regarding smoking and the duration of diabetes, which are important variables in the analysis of CHD risk, was lacking. There was a selection bias in this study: the participants were selected from a group of patients who were admitted for the control of hyperglycemia so that they were uniformly hyperglycemic as a group. We did not analyze atherosclerosis of the carotid artery, which was correlated with the presence of coronary artery stenosis in Japanese patients with diabetes\cite{27}. Due to these limitations of our study, the relationship between hyperglycemia and CHD might have been obscured.

In conclusion, non-HDL-C was the most prominent risk factor for the development of CHD in patients with T2DM in this study. In this population, dyslipidemia appeared to be more important than non-lipid variables for the development of CHD. A preventive strategy for CHD in patients with diabetes may be better formulated with the incorporation of non-HDL-C values.

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**Conflicts of Interest**

None.

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