Impact of Prediabetic Status on Coronary Atherosclerosis

A multivessel angioscopic study

OBJECTIVE—To determine if prediabetes is associated with atherosclerosis of coronary arteries, we evaluated the degree of coronary atherosclerosis in non-diabetic, prediabetic, and diabetic patients by using coronary angioscopy to identify plaque vulnerability based on yellow color intensity.

RESEARCH DESIGN AND METHODS—Sixty-seven patients with coronary artery disease (CAD) underwent angioscopic observation of multiple main-trunk coronary arteries. According to the American Diabetes Association guidelines, patients were divided into non-diabetic (n = 16), prediabetic (n = 28), and diabetic (n = 23) groups. Plaque color grade was defined as 1 (light yellow), 2 (yellow), or 3 (intense yellow) based on angioscopic findings. The number of yellow plaques (NYPs) per vessel and maximum yellow grade (MYG) were compared among the groups.

RESULTS—Mean NYP and MYG differed significantly between the groups (P = 0.01 and P = 0.047, respectively). These indexes were higher in prediabetic than in non-diabetic patients (P = 0.02 and P = 0.04, respectively), but similar in prediabetic and diabetic patients (P = 0.44 and P = 0.21, respectively). Diabetes and prediabetes were independent predictors of multiple yellow plaques (NYPs ≥2) in multivariate logistic regression analysis (odds ratio OR 10.8 (95% CI 2.09–55.6), P = 0.005; and OR 4.13 (95% CI 1.01–17.0), P = 0.049, respectively).

CONCLUSIONS—Coronary atherosclerosis and plaque vulnerability were more advanced in prediabetic than in non-diabetic patients and comparable between prediabetic and diabetic patients. Slight or mild disorders in glucose metabolism, such as prediabetes, could be a risk factor for CAD, as is diabetes itself.

Diabetes mellitus is well known to be associated with an increased risk of mortality resulting from advanced systemic and cardiovascular atherosclerosis (1,2). In addition, there is growing evidence that non-diabetic levels of glucose metabolism, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) with a high risk for the development of diabetes are also related to an elevated risk of cardiovascular events and a poor prognosis (3,4). Recently, the American Diabetes Association (ADA) guidelines defined these categories, including IFG, IGT, or an HbA1c value in the range of 5.7–6.4%, as prediabetes (5). However, the morphology, vulnerability, and distribution of coronary atherosclerosis in prediabetic patients have not yet been fully validated. Coronary angioscopy is a useful imaging modality for assessing the characteristics of atherosclerotic plaques in vivo.

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was based on the ADA guidelines (5). Diabetes was defined as a fasting plasma glucose (FPG) concentration of $\geq 126$ mg/dL, self-reported clinician-diagnosed diabetes or an HbA1c level of $\geq 6.5\%$ (National Glycohemoglobin Standardization Program). Prediabetes was defined as an FPG concentration of 100–125 mg/dL or an HbA1c level of 5.7–6.4%. Nondiabetes was defined as an FPG concentration of <100 mg/dL and an HbA1c level of $\leq 5.6\%$. The value of HbA1c (Japan Diabetes Society +0.4%) was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated using the appropriate formula (14). The medical ethics committee at Nippon Medical School Chiba-Hokusoh Hospital approved this study protocol, and written informed consent was obtained from all patients before the catheterization procedures.

**Angioscopic imaging and analysis**

The coronary angioscopic procedure has been reported previously (6–11). Coronary arteries with proximal tortuosity, sharp angle, calcification, or ostial stenosis were not performed because of the expected difficulty in acquiring angioscopic images for the entire vessel. Before observation, the white balance was adjusted for color correction. The light power was adjusted to avoid reflection and obtain images with adequate brightness for determination of the plaque color. During angioscopic observations, an assistant adjusted the light power to maintain a constant brightness level on the target plaque. Angioscopic images and fluoroscopy during the angioscopic observations were recorded simultaneously on videotape for later analysis. The yellow grade was classified semiquantitatively according to the surface color as: 0, white; 1, light yellow; 2, yellow; and 3, intense yellow. Yellow plaque was defined simply as a yellow area on the luminal surface. The number of yellow plaques (NYPs) was determined for each vessel observed and averaged per vessel. The existence of MYPs was defined as NYPs $\geq 2$ in at least one observed vessel. A ruptured plaque was considered to be a wall irregularity, including a tear, flap, or ulceration on the plaque surface. A thrombus was defined as a coalescent red superficial or protruding mass adhering to the vessel surface, but clearly a separate structure that remained after flushing with Ringer lactate. A representative case is shown in Fig. 1.

**Statistical analysis**

All statistical analyses were performed using SPSS software (version 11.0.1; SPSS Inc., Chicago, IL). Categorical variables are presented as frequencies, and these were compared using the Pearson $\chi^2$ test. Continuous quantitative data were presented as mean values $\pm SD$. All variables were evaluated with ANOVA and the least significant difference statistical methods. Univariate logistic regression analysis was used to determine the clinical predictors (age, sex, other coronary risk factors, clinical presentation, medication, and laboratory data) for MYPs. Prediabetes and diabetes were categorized in each group as a reference of the nondiabetic group. Three values of prediabetes, diabetes, and LDL cholesterol (LDL-C) that achieved significant levels ($P < 0.05$) in a univariate logistic regression analysis were tested for their independent association with MYPs in a multivariate logistic regression model. All differences were evaluated at the 95% level of significance ($P < 0.05$).

**RESULTS**

**Patient characteristics**

The clinical characteristics of the 67 patients are summarized in Table 1. Nondiabetes was diagnosed in 16 patients (24%), prediabetes in 28 patients (42%), and diabetics in 23 patients (34%). In the diabetic group, 2 patients (9%) were taking oral hypoglycemic agents, whereas 7 patients (30%) were on diet therapy alone. Most parameters did not differ between the groups, the exceptions being serum FPG, HbA1c, and C-reactive protein (CRP) levels. Mean levels of FPG and HbA1c were higher in patients with prediabetes and diabetes than in nondiabetic patients (92 ± 5 vs. 102 ± 9 vs. 138 ± 36 mg/dL, $P < 0.001$; 5.2 ± 0.3 vs. 5.7 ± 0.4 vs. 7.4 ± 1.3%, $P < 0.001$; respectively). CRP levels were higher in the diabetic group than in the prediabetes and nondiabetic groups (0.14 ± 0.17 vs. 0.13 ± 0.10 vs. 0.30 ± 0.32 mg/dL, $P = 0.012$). Statins were prescribed equally in 63% of patients with nondiabetes, 64% of patients with prediabetes, and 70% of patients with diabetes ($P = 0.90$). As a result, mean levels of LDL-C were similar among the three groups (121 ± 28 vs. 124 ± 28 vs. 111 ± 33 mg/dL; $P = 0.28$).

**Angioscopic findings**

The angioscopic characteristics of the 67 patients at baseline are also shown in Table 1. The distributions of the coronary arteries observed were similar in the three groups. Total yellow plaque number and yellow intensity differed significantly among the three groups ($P < 0.01$ and $P = 0.04$, respectively). No significant differences were observed in the frequency of plaque rupture and thrombus ($P = 0.89$ and $P = 0.50$, respectively). MYPs were less prevalent in the nondiabetic group than in the prediabetes and diabetic groups (31 vs. 64 vs. 74%, respectively; $P = 0.023$). Both average NYPs per vessel and the maximum yellow grade (MYG) per coronary artery are shown in Fig. 2. These values also showed significant differences between the nondiabetes and the other two groups (0.80 ± 0.64 vs. 1.45 ± 0.81 vs. 1.63 ± 0.99, $P = 0.011$; and 1.44 ± 1.03 vs. 2.00 ± 0.86 vs. 2.30 ± 0.70, $P = 0.047$; respectively). More

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**Figure 1** — Representative case with prediabetes diagnosis. No angiographic stenosis was observed in the right coronary artery (A), whereas an intramural red thrombus was observed at the proximal site (B), and three yellow plaques were identified on angioscopy (B–D). The yellow intensity of these plaques was defined as grades 1, 2, and 1, respectively. Significant stenosis was not observed in the left circumflex artery (E), whereas two yellow plaques were defined as grades 1 and 2, respectively (F and G). A 50% stenosis and a 90% stenosis were identified on angioscopy in the middle part of the left ascending artery (H). According to angioscopic findings, both these lesions were evaluated as grade 3 yellow plaques (I and J). In this case, the average NYP was 2.33 (seven yellow plaques in three vessels), and the MYG was 3.
specifically, the NYP in the prediabetic group was greater than that in the non-diabetic group \( (P = 0.017) \), whereas it was similar to that in the diabetic group \( (P = 0.44) \). Similarly, the MYG in the prediabetic group was greater than that in the non-diabetic group \( (P = 0.040) \), whereas it was similar to that in the diabetic group \( (P = 0.21) \). Univariate logistic regression analysis (Table 2) showed that prediabetic, diabetic, and LDL-C levels were significantly associated with an increased risk of MYPs \( (P = 0.039, P = 0.011, \text{and} \ P = 0.022, \text{respectively}) \). These three variables were not attenuated in multivariate analysis (prediabetes: odds ratio \([OR]\) 4.13 \([95\% CI 1.01–17.00], P = 0.049\); diabetes: \( OR \) 10.8 \([95\% CI 2.09–55.56], P = 0.005\); and LDL-C: \( OR \) 1.03 \([95\% CI 1.01–1.05], P = 0.006\).
degree of yellow intensity was negatively correlated with the thickness of fibrous cap (10). Thus, the total NYPs represents the proliferation of coronary atherosclerosis overall, whereas the intensity of the yellow color reflects the plaque vulnerability. Because the average NYP and MYG were equivalent in both prediabetic and diabetic patients, patients with an early stage of glucose metabolism disorder may be likely to have advanced coronary atherosclerosis and be vulnerable to cardiovascular events. A pivotal prospective angioscopic investigation reported that the existence of MYPs (NYPs per vessel of ≥2) predicted future cardiac events (12). In our study, prediabetes, diabetes, and LDL-C were significant predictive factors for the existence of MYPs. Serum LDL-C concentration is known to affect the plaque component and volume (27,28). Lipid-lowering statin therapy has been found to reduce the intensity of the yellow plaque color, whereas the regression of the yellow intensity was positively correlated with the decrease in LDL-C on the basis of an angioscopic investigation (9). Consequently, patients with high values of LDL-C are likely to show many yellow plaques on angioscopy. Notably, not only diabetes but also prediabetes was a significant factor in the prediction of MYPs. The findings of a meta-analysis of randomized trials that enrolled a total of 23,152 patients with IGT and IFG are interesting (29). This study divided the population into two groups: aggressive medical treatment to prevent the progression of diabetes and no treatment. Then, they compared the clinical outcomes. Although the medical treatment group showed a significant reduction in future diabetes rates, the all-cause and cardiovascular mortalities were not reduced in comparison with controls. This result may be explained by our finding of equal atherosclerotic proliferation in the prediabetic and diabetic groups.

**Limitations**

The current study has several limitations. First, data comprise a retrospective analysis of patients in whom whole images of multivessel coronary arteries by angioscopy can be obtained. Second, the findings are from a single center and derived
cardiac events in patients with an early ages. Therefore, some selection bias is required to create a basis for risk. Further clinical investigations will likely to be more vulnerable than patients with prediabetes and diabetes and primary atherosclerosis is equivalent in patients with acute coronary disorders. Lancet 1991;337:809–812

In summary, the present angioscopic study indicates that the degree of coronary atherosclerosis is equivalent in patients with prediabetes and diabetes and that the former set of patients are therefore likely to be more vulnerable than individuals with normal glucose metabolism. Further clinical investigations will be required to create a basis for risk stratification and prevention of future cardiac events in patients with an early stage of glucose metabolism disorder.

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O.K. contributed to the study design and data collection, analyzed the collected data, and wrote the manuscript. M.T. contributed to the study design and data collection and wrote and revised the manuscript. M.Y. contributed to the study design and data collection, analyzed the collected data, and wrote and revised the manuscript. A.S., N.Ki. T.I., N.Ko., R.M., D.M., S.I., K.O., and T.O. contributed to data collection. C.I., N.H., Y.S., and K.M. revised the manuscript. All authors read the manuscript and approved the submission. M.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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