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NEWLY DEVELOPED DIABETIC RETINOPATHY AND ITS PRECEDING CHANGES IN BIOLOGICAL MARKERS

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ABSTRACT

To disclose the chronological changes prior to the manifestation of diabetic retinopathy (DR), we analyzed the time course of biological markers among apparently healthy diabetic subjects in a case-control study of 21,579 adults who had undergone comprehensive health examinations for ≥ 10 years. We identified 54 cases who had newly developed DR, and selected 108 adults without fundus abnormalities, matching them for sex, age, and fasting plasma glucose (FPG) at the onset of the patient group's retinopathy as a referent group from the same population. In a multivariate analysis, a high average FPG (> 175 mg/dl) and a final-year FPG reduction (< −3%) were significantly associated with a 5.4 (95% CI, 1.8−15.7)- and 5.0 (95% CI, 1.0−24.7)-fold increased risk of DR, respectively. Thus, we surmised that sustained hyperglycemia and a subsequent drop in FPG might promote retinopathy in non-insulin dependent diabetes mellitus.

INTRODUCTION

Retinopathy is one of the major chronic complications of diabetic patients and is the leading cause of severe vision loss.[1-3] It is well known that sustained hyperglycemia promotes the onset of diabetic retinopathy (DR) among patients with both insulin dependent diabetes mellitus (IDDM)[4-11] and non-insulin dependent diabetes mellitus. (NIDDM)[12-15] Recent clinical trials have clearly shown that good glycemic control can prevent the onset of DR for IDDM,[16,17] but there is little data available for NIDDM.[18] Moreover, how DR develops in connection with chronological changes in glycemic status over a period of time is poorly understood. In this study, we analyzed the time course of plasma glucose and other biological markers prior to the manifestation of retinopathy among apparently healthy diabetic men and women in a case-control study.

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METHOD

Subjects

From 1971 to 1992, 21,579 adults have regularly participated in automated multiphasic health testing for more than 10 years at the Aichi Prefectural Health Care Center, Nagoya, Japan. Most participants are office workers in Nagoya City and its vicinity who are required to have a medical checkup annually at the expense of their employers in accordance with the Industrial Safety and Health Law.[19] At the Center, each participant routinely underwent a series of laboratory screening tests including a fundoscopic examination, and was given medical advice based on the test results.

The subjects of the present study were 48 men and 6 women (mean age $\pm$ SD, 52.8 ± 6.7) recruited from the above-mentioned population who had newly developed diabetic retinopathy, and whose previous health checkup data were available at least every other year for 5 years prior to the onset of retinopathy (DR subjects). As a referent group, we randomly selected 96 males and 12 females (non-DR subjects) from the same population, who had never shown any fundoscopic abnormality and were individually matched for sex, age and fasting plasma glucose (FPG) level at the onset of retinopathy in the DR subjects. Nineteen DR subjects (33%) and 47 non-DR subjects (41%) received oral antihyperglycemic agents. Antihypertensive medications were taken by six DR (11%) and 10 (8.7%) control subjects. However, detailed information on medication was not available.

Laboratory examinations

Color fundus photographs were taken for a standard central field of only one eye of each participant at an angle of 45 with the Canon CR-45NM or CR4-45NM non-mydriatic fundus cameras (Canon Inc, Tokyo, Japan). They were independently assessed by three well-trained ophthalmologists without any clinical information for this study. Diabetic retinopathy was defined as the presence of one or more microaneurythms, blot hemorrhages, or exudates.[20-23] Subjects had neither proliferative retinopathy nor photocoagulation during this study period.

Blood pressure was automatically measured with a mercury sphygmomanometer while the subject adopted a supine position. Systolic (SBP) and diastolic (DBP) blood pressure were defined as the level of Swan's first and fifth point, respectively. Body mass index (BMI) was defined as the weight in kg divided by the square of height in meters (kg/m^2). Venous blood was sampled from fasting participants and immediately analyzed for FPG and total cholesterol (TC) by an in-house chemical autoanalyzer. When the autoanalyzer was replaced with a new one, hundreds of blood samples were examined by the old and new machines simultaneously, and a conversion formula was computed for each blood marker. All values obtained by the old machine were then expressed as new ones for this study. Administration of drugs was stopped $\geq$ 14 hours before blood measurement.

Statistical analysis

We defined the year when retinopathy was first observed as 'year 0' in each case, and traced patients' laboratory data for 5 years prior to the onset.[24] Annual group mean values for FPG, TC, BMI, SBP and DBP were compared between the two groups by the unpaired *t*-test. Five-year average values of these variables were also examined. Logistic regression analysis was applied to assess the relationship of these factors with DR.[25] For this analysis, DR subjects were divided into three subgroups according to the tertile of non-DR subjects for each variable. The statistical package SAS (SAS Institutes, Cary, NC, USA) was used to process the data.

RESULTS

Time course of biological markers

The time course of FPG for the DR and non-DR subjects is shown in Figure 1. FPG of non-DR subjects increased linearly year by year from 141 mg/dl in year −5 to 199 mg/dl in year 0. FPG of DR subjects, however, sustained significantly higher levels than that of non-DR subjects until year −1. After increasing from 193 mg/dl in year −3 to 217 mg/dl of year −1, FPG in DR subjects decreased to 209 mg/dl in year 0. Divided by medication status, anti-hyperglycemic drug takers and non-takers showed quite similar patterns, although FPG of drug takers remained lower by 6−18 mg/dl than that of non-takers during the period.

Mean SBP was 129 mm Hg in year −5 and increased to 135 mm Hg in year 0 in DR subjects, while changing from 125 to 128 mm Hg over five years in non-DR subjects (Figure 2). Thus, SBP was slightly higher in DR subjects than in non-DR subjects, but the difference was not statistically significant before the manifestation of DR. Mean DBP (not shown in the figure) was quite similar in both groups, increasing from 80 to 82 mm Hg in DR subjects and from 79 to 80 mm Hg in non-DR subjects during the period (no significant difference between the groups was observed in any year).

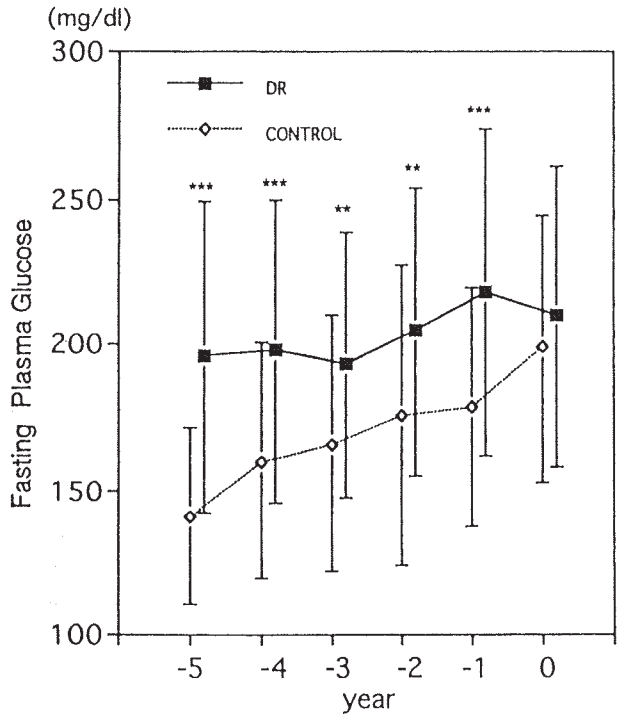

Figure 1. Serial changes in fasting plasma glucose in 54 subjects who subsequently developed diabetic retinopathy (DR) and the corresponding values of 108 control subjects. The years are listed on the abscissa, with year 0 used for the year of DR onset. Values shown are means ± SD.
** $p < 0.01$; *** $p < 0.001$.

Mean TC (figure not shown) was 216 mg/dl in DR subjects and 202 mg/dl in non-DR subjects in year −5 (not a significant difference). The values gradually increased in both groups, and their chronological changes were almost identical (211 mg/dl in DR subjects and 216 mg/dl in non-DR subjects in year 0). BMI (figure not shown) slightly decreased in both groups: from 24.5 to 23.8 kg/m^2 in DR subjects and from 24.9 to 23.8 kg/m^2 in non-DR subjects over the five years.

Average value of biological markers for 5 years

Five-year average values were calculated for FPG, SBP, DBP, TC and BMI. FPG of DR subjects averaged 202 mg/dl and was significantly higher than the 163 mg/dl of non-DR subjects ($p < 0.001$). The five-year averages of SBP/DBP, TC, and BMI (DR subjects vs non-DR subjects) were 130/81 vs 126/79 mm Hg, 207 vs 207 mg/dl, and 24.2 kg/m^2 vs 24.3 kg/m^2, respectively, showing no significant differences between the two groups.

Logistic regression analysis

We found significant differences in five-year average FPG and changes in FPG from year −1 to 0 between DR subjects and non-DR subjects. To clarify the manner of association of these factors with DR, we performed a logistic regression analysis adjusting for sex, age, and FPG in year 0 (Table 1).

High average FPG (> 175 mg/dl) was associated with an appreciably increased risk of developing DR (odds ratio=5.4; 95% CI, 1.8−15.7), and mid-average FPG (145−175 mg/dl) with an intermediately high risk (odds ratio=2.0, 95% CI, 0.8−5.5), compared with a low risk of < 145 mg/dl. It yielded a significant linear trend (p=0.02). A final-year FPG reduction (% change in FPG from year −1 to 0, < −3%) was related to a 5-fold greater risk (95% CI, 1.0−24.7; p=0.05) than for an unchanged FPG (changes, within ±3%). A final-year FPG elevation (changes, > +3%) was also associated with an increased risk (odds ratio=2.1; 95% CI, 0.5−8.7), although it was statistically insignificant.

DISCUSSION

Most diabetic patients do not notice the onset of their retinal abnormalities. Then, only periodic health checkup might serve to detect the early stages of DR. We examined the time course of laboratory data before the onset of DR for the first time, and found that sustained hyperglycemia primarily increased the risk of developing DR. This conclusion is consistent with the findings of most previous epidemiological studies,[11-13] in that, the glycemic status at the baseline and duration of diabetes was associated with an increased risk of retinopathy.

We also demonstrated that a drop in FPG was strongly associated with the manifestation of DR. According to recent clinical trials for IDDM, a transient deterioration of retinopathy was observed after starting intensified treatment by continuous subcutaneous insulin infusion.[26-32] For NIDDM, Henricsson et al.[33] showed an association between a reduction in HbA1c caused by insulin therapy and a progression of DR. In these reports, it was uncertain whether it was the FPG decrease or the insulin supplementation that did harm. Despite the fact that no subjects in our study received insulin therapy although some took oral agents instead, the time course of FPG was quite similar between drug takers and non-takers. Therefore, it is more likely that FPG reduction itself triggers the onset of DR. Clinical and experimental studies showed that retinal blood flow increased in early and uncontrolled diabetes.[34-36] Increased blood flow damaged the vascular endothelium[37] and thickened the basement membrane, resulting in vascular sclerosis

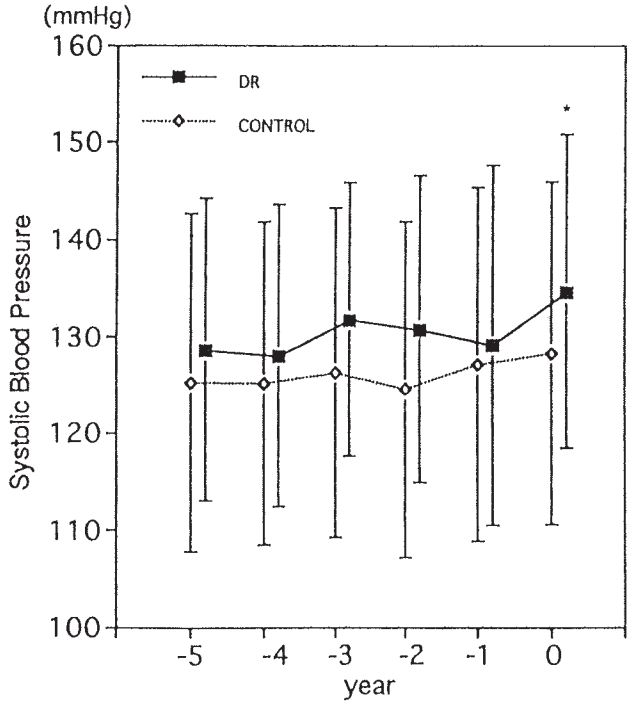

Figure 2. Serial change in systolic blood pressure in DR subjects and controls. Definitions are the same as Figure 1. * $p < 0.05$.

Table 1. Association of five-year averaged fasting plasma glucose and final year plasma glucose change with the development of diabetic retinopathy. Multivariate analysis using logistic model.

Factor	Category		No of subjects		Odds Ratio (95% CI)	P-Value	Trend-p
			DR (n=42)	non-DR (n=86)			
Averaged fasting plasma glucose for 5 years	Low	(< 145 mg-dl)	6	28	1.00		
	Middle	(145–175 mg/dl)	6	28	2.02 (0.75– 5.48)	0.17	
	High	(175 mg/dl <)	30	30	5.37 (1.84–15.68)	<0.01	0.02
% change in fasting plasma glucose from year −1 to year 0	Decreased	(< −3%)	22	20	4.96 (1.00–24.70)	0.05	
	Unchanged	(−3% – +3%)	3	13	1.00		
	Increased	(+3% <)	17	53	2.05 (0.48– 8.69)	0.33	

Age, sex, plasma glucose level at year 0 are adjusted.

and poor vascular reactivity. A rapid decrease in FPG after long-standing hyperglycemia might restrict retinal perfusion whose autoregurability was already lost, and cause ischemic lesions. Although the mechanism is not clear in more detail to avoid the onset of DR is not clear in more detail, we believe it is better to control glycemic status cautiously so as not to accumulate a glycemic overload.

Blood pressure was slightly higher in DR subjects than in non-DR subjects, but the difference did not reach statistical significance. Effects of hypertension on retinopathy has not been fully discussed,[38] whereas those on nephropathy are well established.[39,40] One plausible explanation is the effect of insulin resistance which could cause both hyperglycemia and hypertension.[41] Whether hypertension promotes DR should be further investigated. TC increased and BMI decreased gradually until DR became manifest, but the time course of these variables was not essentially different from that of non-DR subjects. Some investigators suggested that hypercholesterolemia[42,43] and either obesity[12] or leanness[44] were the risk factors for DR. However, the associations between lipid metabolism and DR is not conclusive in this study.

There may be some shortcomings in this study. First, participants were examined for the single field of one eye only, without papillary dilation in this health checkup. Even if one should fail to detect the unilateral or marginal retinopathy,[45] the differences between DR and non-DR subjects would be less marked because part of the DR would be included in the non-DR; thus, the DR and non-DR risk obtained in the present investigation would be underestimated in relation to the actual risk. Second, we used a FPG concentration which was measured once a year as an index of glycemic status. It was, therefore, unclear in which year for how long or how often FPG was lowered prior to the onset of DR. Plasma glucose concentration is known to vary with recent activity levels, food eaten, and time of day. Glycated haemoglobin is more stable and could be better than plasma glucose in assessing long-term blood glucose control,[46] but information on this marker was not available in time for use in our study. A number of previous studies have demonstrated that the duration of diabetes mellitus (DM) is one of the most important factors for the development of DR. However, it is too difficult to detect the exact onset of DR in NIDDM, so we did not include it as a variable in our models. Finally, all diabetic participants were repeatedly advised to improve their lifestyles at their health checkups, and some received medical treatments including antihyperglycemic agents. The frequency of the medication for hyperglycemia and hypertension was, however, similar between DR and non-DR subjects, thus assuring that the influence of therapeutic status would be minimized. Lifestyle modification could also have affected the time course of a glycemic condition and the occurrence of diabetic complications. These effects will be examined in our ongoing intervention trials.

In conclusion, sustained hyperglycemia and its subsequent improvement might promote the onset of retinopathy in NIDDM. It is suggested that modest glycemic control before reaching severe hyperglycemia is a key to preventing the onset of DR. Since our retrospective observations could not accurately determine the target plasma glucose level which should be maintained, further longitudinal observations are warranted to confirm this strategy.

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