Table 1—*Incidence of brain infarction in 3 groups of diabetic patients with and without retinopathy*

Retinopathy type	Brain infarction
Asymmetric	5*/12 (41.7%)
Symmetric	5/65 (7.7%)
Negative	5/65 (7.7%)

*$P < 0.005$, patients with asymmetric retinopathy vs. those with symmetric retinopathy and without retinopathy by χ^2 analyses.

presence of laterality in retinopathy was defined when >2 grades difference were found between eyes in a patient. Fluorescent angiography was made in some cases to determine whether retinopathy was preproliferative or proliferative.

A total of 15 patients developed brain infarction during the follow-up period. As shown in Table 1, the percentage of brain infarction in patients with asymmetric retinopathy was 41.7% (5 of 12), which was significantly higher than 7.7% in patients with symmetric retinopathy or 7.7% in patients without retinopathy. The laterality of brain infarction determined by CATscan coincided with that of the worse side of asymmetrical retinopathy in 4 of 5 patients.

No differences were observed in sex, age, duration of diabetes, BP, BMI, fasting blood glucose, HbA_1 or serum lipid levels among the 3 groups in 1981. In some cases, asymmetry of retinopathy disappeared during the follow-up period. The asymmetry of retinopathy significantly persisted in 42% of patients who had asymmetry at the starting point and throughout the follow-up period. This contrasted with the 4% of patients who had a new appearance of asymmetry in symmetric retinopathy ($P < 0.001$).

By the multiple regression analysis for the incidence of brain infarction in 77 patients with retinopathy, male sex and fundoscopic laterality indicated a significantly high risk for brain infarction (t values are 1.76 and 2.24, respectively). However, age, sBP, and HbA_1 were not associated with the incidence of brain infarction.

The laterality of retinopathy in our cases was observed significantly more repetitively compared with symmetric retinopathy patients. Therefore, some extraocular factors such as arteriosclerosis or anomaly of carotid-brain vasculature may persist in diabetic patients with asymmetric retinopathy and may accelerate the diabetic retinopathy. This acceleration may be uneven in each side of the eyes, because in our cases the site of brain infarction coincided with that of retinopathy. We conclude that laterality of diabetic retinopathy is one of the predictors for brain infarction development in patients with diabetes mellitus.

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BP, blood pressure; sBP, systolic blood pressure; BMI, body mass index; IDDM, insulin-dependent diabetes mellitus.

References

1. Browning DJ, Flynn HW, Blankenship GW: Asymmetric retinopathy in patients with diabetes mellitus. *Am J Ophthalmol* 105:584–89, 1988
2. Sebag J, Feke GT, Deloli FC: Effects of inner retinal degeneration on retinal blood flow and oxygen extraction (Abstract). *Ophthalmology* 94(Suppl.):83, 1987
3. Becker B: Diabetes mellitus and primary open-angle glaucoma. *Am J Ophthalmol* 71:1–16, 1971
4. Sivalingam A, Brown GC, Magargal LE, Menduke H: The ocular-ischemic syndrome. II. Mortality and systemic morbidity. *Int Ophthalmol* 13:187–91, 1989
5. Scott GI: Ocular complications of diabetes mellitus. *Br J Ophthal* 37:705–15, 1953

Effect of Eicosapentaenoic Acid Ethyl on Urine Albumin Excretion in NIDDM

Fish oil, rich in n-3 fatty acid (EPA and DHA), has properties that help prevent development of atherosclerosis and thrombosis (1). Dietary cod-liver oil partially normalized increased microvascular albumin leakage in diabetic patients with albuminuria (2). EPA is useful in stopping the progression of IgA nephropathy (3). The effect of purified EPA on albuminuria was examined in NIDDM patients with albuminuria.

The subjects in this study were 10 male and 14 female NIDDM patients with albuminuria. The average age was 63.9 ± 2.8 yr. The average duration of diabetes mellitus (after diagnosis) was 9.8 ± 1.2 yr. Patients were treated with diet therapy only (8.3%), oral sulfonylurea administration (58.4%), or conventional insulin therapy (33.3%). Diabetic retinopathy was found in 41.7% of patients and 16.7% of the patients combined with diabetic neuropathy. In 37.5% of the patients, hypertension was observed and BP levels were controlled by antihypertensive agents. The dose of these agents and diet composition were not changed. According to the average UAI (mg/g Cr) of two timed collections obtained at the same time, all patients were divided into two groups: group 1: 30 mg/g Cr<UAI<300 mg/g Cr, group 2: UAI>300 mg/g Cr.

The capsule of EPA-E, 900 mg/

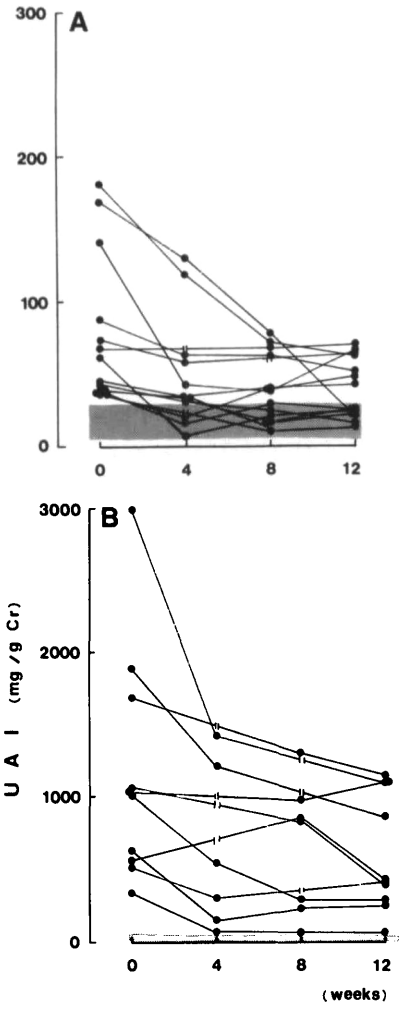

Figure 1—*Chronological changes of UAI (mg/g Cr) for 12 wk after the start of EPA-E administration in group 1 (A) and group 2 (B). NIDDM patients in groups 1 (n = 14; 30<UAI<300 mg/g Cr) and 2 (n = 10; UAI>300 mg/g Cr) had albuminuria and overt albuminuria, respectively. The shadow shows the normal range of UAI.*

day, was administered orally 3 times/day after each meal. Each capsule contained a 90% pure ethyl ester of 300 mg with 0.2% α-tocopherol. EPA-E administration continued for 12 wk, and changes of the UAI were observed every 4 wk.

EPA-E immediately reduced the UAI in group 1 (Fig. 1A). The reduction of the UAI was observed in 71.4% of patients treated with EPA-E, and its effect continued for 12 wk. The effect of EPA-E on the UAI, determined by paired Student's *t* test, was statistically significant ($P < 0.01$). Of the patients, 50% showed normalization of UAI by 12 wk after the start of EPA-E treatment. EPA-E also improved UAI in 70% of the patients in group 2 (Fig. 1B). The effect of EPA-E was significant ($P < 0.01$) in group 2. No patients showed obvious progression of UAI.

No side-effects of EPA-E administration were observed. EPA-E administration for 12 wk did not affect serum total cholesterol, HDL-cholesterol, or triglyceride levels. No changes were observed in plasma glucose, HbA_{1c}, or BP levels by EPA-E.

EPA blocks TXA_2 production in human platelets, inhibits the release of arachidonic acid from membrane phospholipid, and reduces arachidonic acid metabolism by cyclooxygenase-dependent pathway (4–6). Platelet activation contributes to the pathogenesis of microvascular complications of diabetes mellitus (7). Recent findings suggest that picotamide, a dual TXB synthase inhibitor and TXB receptor antagonist, reduces exercise-induced albuminuria in microalbuminuric NIDDM patients (8). This may indicate an involvement of TXB in diabetic nephropathy. Therefore, the effect of EPA-E on albuminuria may be mediated by the reduced production of TXA_2.

In conclusion, EPA-E at a small dosage, which does not affect lipid metabolism, reduces urinary albumin excretion in NIDDM patients.

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EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; NIDDM, non-insulin-dependent diabetes mellitus; BP, blood pressure; UAI, urine albumin index; Cr, creatinine; EPA-E, eicosapentaenoic acid ethyl; IgA, immunoglobulin A; HDL, high-density lipoprotein; TXA_2, thromboxane A_2; TXB, thromboxane B.

References

1. Kromhout D, Bosschieter EB, de Lezenne Coulander C: The inverse relation between fish assumption and 20-year mortality from coronary disease. *N Engl J Med* 312:1205–09, 1985
2. Jensen T, Stender S, Goldstein K, Holmer G, Deckert T: Partial normalization by dietary cod-liver oil of increased microvascular albumin leakage in patients with insulin-dependent diabetes and albuminuria. *N Engl J Med* 321:1572–77, 1989
3. Hamazaki T, Tateno S, Shishido H: Eicosapentaenoic acid and IgA nephropathy. *Lancet*:1017–18, 1984
4. Hirai A, Terano T, Hamazaki T, Sajiki J, Kondo S, Ozawa A, Fujita T, Miyamoto T, Tamura Y, Kumagai A: The effects of the oral administration of fish oil concentrate on the release and the metabolism of [^{14}C] arachidonic acid and [^{14}C] eicosapentaenoic acid by human platelets. *Throm Res* 28:285–98, 1982
5. Terano T, Hirai A, Hamazaki T, Kobayashi S, Fujita T, Tamura Y, Kumagai A: Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. *Atherosclerosis* 46:321–31, 1983
6. Needleman P, Raz A, Minkes MS, Ferrendeli JA, Sprecher H: Triene prostaglandins: prostacyclin and thromboxane biosynthesis and unique biological properties. *Proc Natl Acad Sci USA* 76:944–48, 1979
7. Butkus A, Skrinstka VA, Schumacher OP: Thromboxane production and platelet aggregation in diabetic subjects with clinical complications. *Thromb Res* 19:211–13, 1990
8. Giustina A, Bossoni S, Cimino A, Teresa Comini M, Gazzoli N, Battista Leproux G,

Wehrenberg WB, Romanelli G, Giustina G: Picotamide, a dual TXB synthase inhibitor and TXB receptor antagonist, reduces exercise-induced albuminuria in microalbuminuric patients with NIDDM. *Diabetes* 42:178–82, 1993

The Impact of a Color-Classified HbA_{1c} Graph for Self-Monitoring and Self-Adjustment of Long-Term Glycemic Control

During the previous 4–8 wk (1,2), accumulating evidence has revealed that long-term glycemic control as expressed by HbA_{1c}, the value of which is closely related to the mean level of blood glucose, is closely associated with the progression of diabetic complications (3–5). Thus, HbA_{1c} can serve as the most important marker for long-term glycemic control.

Some difficulties arise when teaching patients about the meaning of HbA_{1c} and the relationship between HbA_{1c} levels and the progression of diabetic complications. Therefore, we attempted to introduce a color-classified HbA_{1c} graph in which the HbA_{1c} level was color-classified according to the relative risk of the HbA_{1c} level on the progression of complications. In this study, it soon became clear that the HbA_{1c} graph allowed patients to visualize their HbA_{1c} levels and, therefore, better understand their conditions. Thus, they were also encouraged to take some positive actions to lower their levels.

From 1989 to 1990, 108 Japanese NIDDM patients were analyzed. They completed a 6-mo follow-up before and after the graph was given without any alteration of the treatment regimen. The NIDDM patients included 48 males and 60 females with a mean age of 59.3 ± 10.2 yr, a mean diabetes duration of 8.5 ± 6.9 yr, and a mean BMI of 23.0 ± 0.3 kg/m^2. All patients had previously received the usual diabetes education program, which included an educational program to show the meaning and significance of HbA_{1c}.

HbA_{1c} was assayed by HPLC on a monthly basis for 1 yr. The normal range of this assay system is 4.5–6.0%. The mean of every 3 mo was calculated and compared both before and after the graph was given.

The color-classified HbA_{1c} graph was color-grouped according to the HbA_{1c} level, which demonstrates the relative risk of long-term diabetic complications with an appropriate color image of the relative risk: HbA_{1c} <6%, green, normal; 6–7%, yellow-green, fair; 7–8%, yellow, risky; 8–10%, red, poor; and >10%, purple, critical (Fig. 1). A monthly recording of HbA_{1c} for 1 yr was possible, and monthly variations of HbA_{1c} levels can be seen at a glance. One month after the graph was given, a patient questionnaire was distributed to examine the psychological and behavioral effect of the graph and to determine whether the graph contributed to an increased awareness of HbA_{1c} or helped motivate patients to obtain better glycemic control.

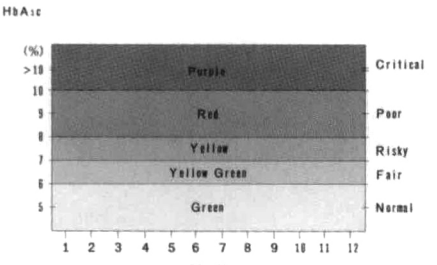

Figure 1—*Color-classified HbA_{1c} graph. The graph was color-grouped according to the level of HbA_{1c}, which demonstrates the relative risk of long-term diabetic complications with an appropriate image of the relative risk: HbA_{1c} <6%, green, normal; 6–7%, yellow-green, fair; 7–8%, yellow, risky; 8–10%, red, poor; and >10%, purple, critical.*

A paired Student's *t* test (BMDP 3D) was done before and after the graph was used. The degree of decrease in the HbA_{1c} level was also compared by either the Wilcoxon rank-sum test or the Kruskal-Wallis test. All statistical analyses were done using the statistical package BMDP XX on an IBM system 3090 computer.

Before the graph was used, only 41% of the patients understood the importance of the HbA_{1c} level, whereas the rate increased to 89% after its use. In addition, only 37% were motivated to improve their HbA_{1c} level before the graph whereas the rate increased to 85% after using the graph. Consequently, the graph users showed evidence of improvement in long-term glycemic control. The improvement in HbA_{1c} was observed independently irrespective of age, sex, duration of diabetes, BMI, control level, or the presence of complications. In addition, poorly controlled patients showed better improvement of HbA_{1c} than fairly well-controlled patients ($P < 0.001$). Of graph users, 69% modified their behavior by either maintaining diet control, increasing exercise, or eliminating alcohol intake.

Surprisingly, ~50% of the patients did not realize the clinical significance of HbA_{1c} before introducing them to the graph. The patients had been taught the meaning of HbA_{1c} during the usual course of the diabetes education program and had been informed about the value of HbA_{1c} during every outpatient visit. This may suggest that the patients were not sufficiently instructed in the importance of HbA_{1c}, even though the normal educational program had been provided. Nevertheless, after observing the color-classified HbA_{1c} graph, they realized the significance of HbA_{1c} as a marker of long-term glycemic control and took some action to improve their HbA_{1c} levels, which resulted in an improvement of hyperglycemia. Indeed, a