

Relation of the Course of Retinopathy to Control of Diabetes, Age, and Therapeutic Agents in Diabetic Japanese Patients

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SUMMARY

Follow-up results of the progression of diabetic retinopathy in 364 patients who attended the Diabetes Clinic of the Third Department of Internal Medicine (University of Tokyo) regularly for more than two years were analyzed in relation to their degree of control, age and therapeutic agents. Ophthalmologic examinations were performed by two ophthalmologists without referring to other data.

In 289 untreated cases, retinopathy at the initial visit was more frequent and more severe when known duration of diabetes was longer and initial fasting blood sugar was higher. The degree of control was judged by fasting blood sugar values determined frequently and regularly. Progression of retinopathy was significantly more frequent in the fair and poor control groups than in the good control group. In older age groups, progression, especially occurrence of new lesions, was more frequent. Sulfonylurea did not appear inferior to insulin so long as an acceptable degree of control was maintained. *DIABETES* 18:773-80, November, 1969.

Vascular disease is the most serious problem faced by the diabetic patient. Whether the patient can be protected from this complication by intensive treatment is not known for certain. Accordingly, a prospective study of diabetic retinopathy in relation to treatment was designed in the Diabetes Clinic of our Department. In this report, the development and progression of lesions during an observation period of two to six years

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are analyzed in relation to the degree of chemical control of diabetes and other factors. Fasting blood sugar values, determined frequently and regularly in all the patients, were adopted as the most reliable index of degree of control. The preliminary data appear to suggest that control delayed the course of retinopathy. Age was another factor influencing the progression of retinopathy. Finally, assessment of usefulness of sulfonylurea therapy for prevention of retinopathy is tried by comparing the result with that of insulin therapy.

MATERIALS AND METHODS

Patients

Three hundred and sixty-four ambulatory patients followed regularly for more than two years in the Diabetes Clinic of the Third Department of Internal Medicine, University of Tokyo, were the subjects of this study. The age and sex distributions at the initial visit are shown in figure 1. The majority of patients had maturity onset type of diabetes.

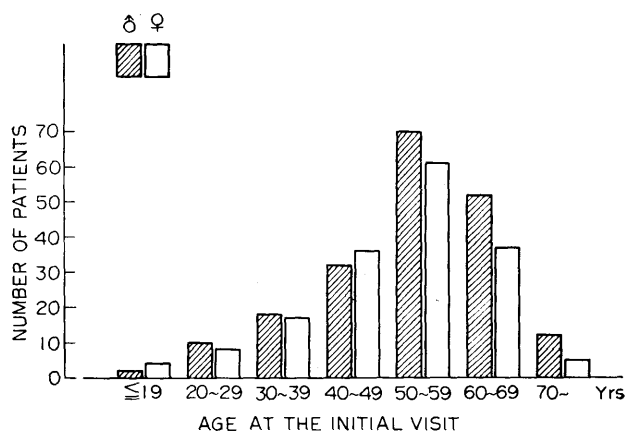


FIG. 1. Age distribution of patients at the initial visit. One hundred and twenty-three of 195 males and ninety-six of 169 females were between fifty and sixty-nine years of age, while thirty males and twenty-eight females were under thirty-nine years.

Criteria of severity and control of diabetes

The fasting blood sugar level was determined twice before starting the treatment except in those cases where immediate therapy seemed desirable. The mean FBS before the treatment was adopted as the index of severity of diabetes.

FBS was determined usually every two to four weeks, except in mild cases with normal FBS who visited less frequently. Eight to twenty determinations per year per patient were made. Blood sugar was determined by Hagedorn-Jensen's method¹ on capillary blood from the ear lobe. This method gives blood sugar values 15 to 20 mg./100 ml. higher than true blood glucose, and FBS levels below 110 mg./100 ml. were regarded as normal.

Degree of control of diabetes was also assessed by the course of FBS levels. Control was defined as "good" when 80 per cent or more of the FBS remained below 140 mg./100 ml. On the other hand judgment of "poor" control was made when more than 50 per cent of the FBS was higher than 170 mg./100 ml. "Fair" control was defined as intermediate between good and poor controls. Mean \pm S.D. of the mean FBS of each patient in the respective groups were: good 127 ± 26 , fair 146 ± 29 , and poor, 167 ± 56 mg./100 ml.

Duration of diabetes

Duration of disease was estimated based on history carefully taken in the Diabetes Clinic. Either occurrence of symptoms attributable to diabetes or, when asymptomatic, recognition of glycosuria or impaired glucose tolerance were, for the purposes of this study, regarded as the onset of disease.

Ophthalmologic examinations

Examinations of the eyes were performed only by Dr. H. Tokuda at the beginning of this study and later by one of the authors (M. F.) in the Department of

Ophthalmology, University of Tokyo, with bilateral dilatation of the pupils and use of magnifying lenses. The eyes were examined at least once a year without the examiner being informed of other clinical data or previous findings before the examination.

After completion of funduscopic examinations, the findings were recorded on a form designed for detailed description. The following criteria were used to determine the stages of diabetic retinopathy taking Wager's classification into consideration: Grade I, either a few microaneurysms or a few small white spots which cannot be attributed to other diseases; Grade II, either waxy exudates or a few hemorrhages with or without associated Grade I changes; Grade III, more numerous hemorrhages and exudates than in Grade II, or angiospastic changes superimposed on the above changes; Grade IV, neovascularization and the presence of marked irregularity in caliber of the veins; Grade V, characterized by the presence of membranous proliferative retinopathy with fibrous ingrowth. Since numbers of patients with Grades IV and V were small, these two were combined for analysis. When grades of retinopathy on both eyes in a patient were different, the severer side was taken as representing the patient. Although the consistency of judgment of the grade of retinopathy was not studied specifically, it was estimated from the record of frequently examined patients that the judgment varied less than once every ten observations and never by more than one grade.

The percentage of patients who showed occurrence of new retinopathy or significant progression of pre-existing lesions affecting the stages defined as above was used as the index of aggravation to compare the difference among groups. The X² test was used to evaluate the significance of difference between groups.¹⁷ Statis-

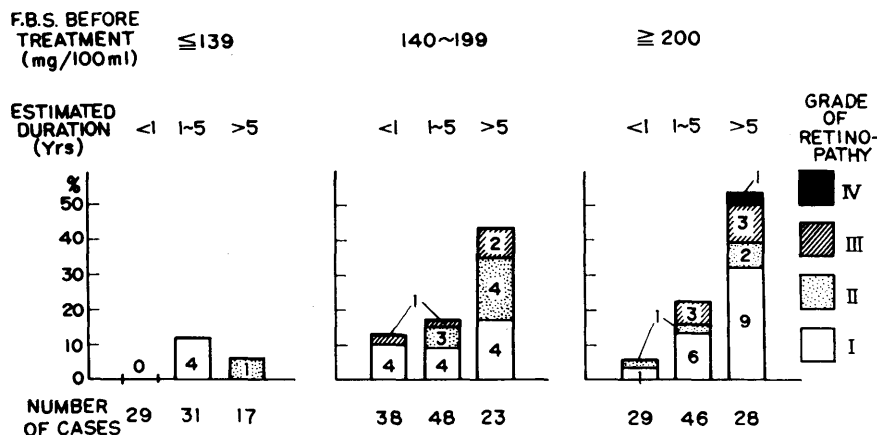


FIG. 2. Frequency and degree of retinopathy at the initial visit. The bars show frequency of retinopathy. The darker areas represent more advanced lesion. Actual numbers of cases are shown in respective areas and the total numbers of cases are shown below. In groups with longer duration and higher fasting blood sugar before treatment, retinopathy tended to be more frequent and severer.

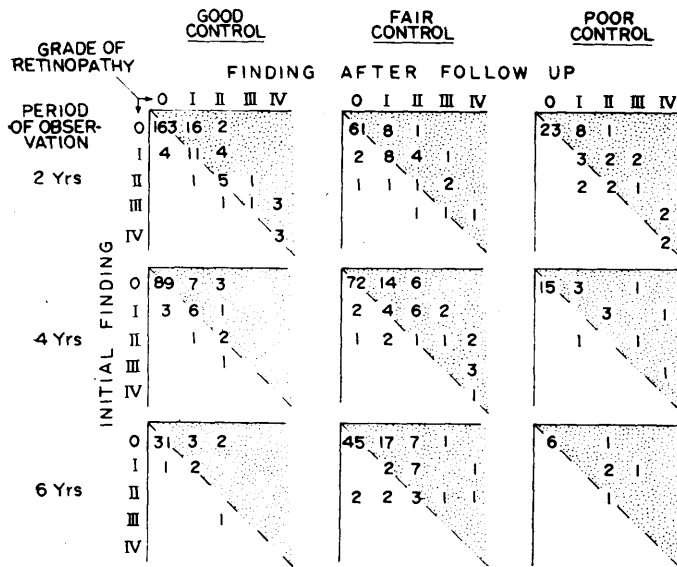


FIG. 3. Comparison of initial versus follow-up findings grouped according to the degree of control. Initial finding (ordinate) is contrasted to the follow-up finding after 2, 4 and 6 years (abscissa). The number of patients who remained at the same degree are found on diagonal broken line. The patients who showed aggravation of retinopathy are found in dotted area.

tical analyses were made among groups who were followed until the same period and not sequentially in the same category. Twenty-two patients have died since the start of the study.

RESULTS

1. The prevalence and degree of retinopathy at the initial visit

The prevalence of retinopathy of 289 untreated cases among 364 patients was analyzed in relation to the initial fasting blood sugar and the estimated duration of diabetes (figure 2). With higher FBS and longer duration, both the frequency and the severity of retinopathy tended to increase. In seventy-seven patients with FBS

lower than 140 mg./100 ml., only one who had duration of more than five years had Grade II retinopathy. In groups with FBS over 170 mg./100 ml. and duration of more than five years, the frequency of retinopathy exceeded 50 per cent, and more severe forms of retinopathy were observed.

2. Progression of retinopathy in relation to the degree of control of diabetes

By February 1967, the numbers of cases followed for 2, 4 and 6 years were 356, 256 and 140, respectively. The observations are summarized in figure 3. The cases are grouped according to the degree of control and periods of observation. Good or poor control for four and six years means that these cases remained

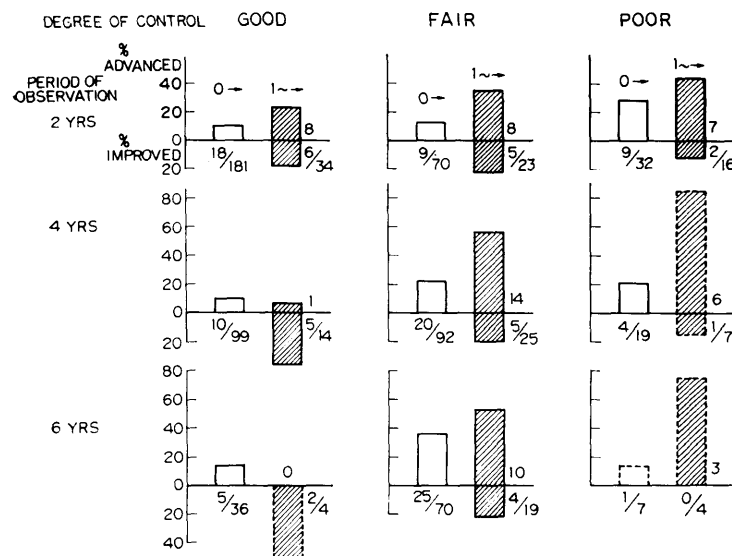


FIG. 4. Correlation of degree of control and progression of retinopathy. Derived from figure 3, the height of bars above the base line depicts percentage of cases who showed progression of retinopathy. Percentage of improvement is shown below the baseline. In each group white bars show frequency of new lesions which appeared during observation and shaded bars show progression or improvement of pre-existing lesion. When the total number of the group is less than ten, the bar is surrounded by broken line. Over-all progression of retinopathy was significantly more frequent in fair plus poor control groups compared with good control groups after 2, 4 and 6 years.

CONTROL OF DIABETES AND PROGRESSION OF RETINOPATHY

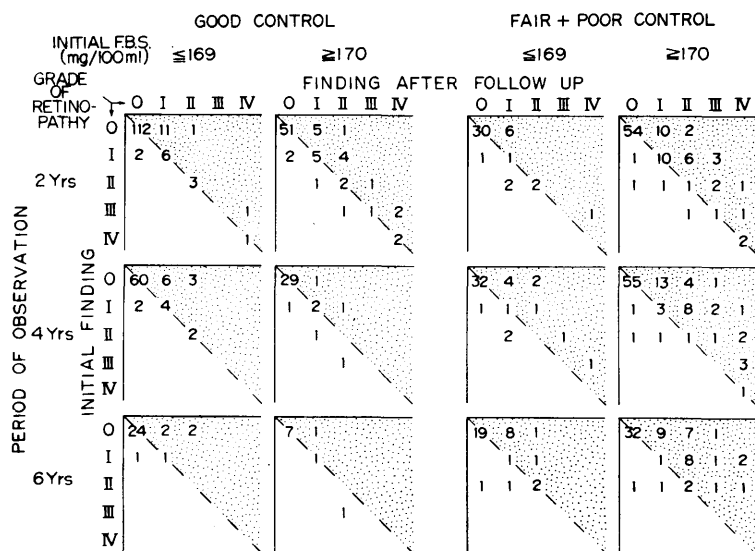


FIG. 5. Follow-up groups with higher and lower fasting blood sugar who later attained different degrees of control. This figure is similar to figure 3 contrasting the initial with the follow-up findings. On the left half, patients who achieved good control were subdivided according to their initial fasting blood sugar. On the right half are shown patients who failed to achieve good control.

in the same control group throughout the total period. Other cases who showed different degrees of control during four or six years were included in the fair control group. In each group, the ordinate shows initial degree of retinopathy while the abscissa shows the retinal findings after 2, 4 or 6 years. Each arabic number in the figure represents the number of cases. For example, in the fair control group followed up for four years, seventy-two cases remained without lesion, while in fourteen and six cases new lesions of Grades I and II developed respectively. On the other hand, Grade I and Grade II retinopathy at the initial visit disappeared after four years of observation in two and one cases. Thus, the numbers in the dotted area represent the

cases in whom new lesions appeared or pre-existing lesions progressed, while those in the white area represent improved cases. The patients with unchanged degree of retinopathy are found on the broken line.

Figure 4 shows the percentage of aggravation in each group of different control during 2, 4 or 6 years. The results indicate that the progression of retinopathy occurred more frequently when the degree of control was poorer. The differences between good and fair plus poor groups were significant by the chi square test ($p < 0.01$, $p < 0.001$ and $p < 0.01$ after 2, 4 and 6 years). This tendency was observed both in the development of new lesions and in the progression of pre-existing retinopathy.

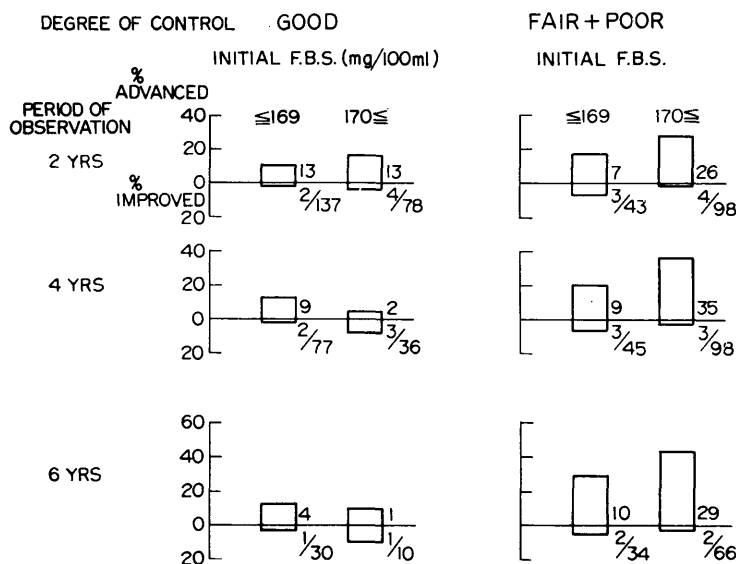


FIG. 6. Effect of degree of control versus initial fasting blood sugar on aggravation of retinopathy. The bars show frequency of over-all progression or improvement of retinopathy as derived from figure 5. The difference between good and fair plus poor control groups was significant after 2, 4 and 6 years. So long as good control was maintained, the aggravation was not more frequent in patients with higher initial fasting blood sugar. In fair plus poor control groups, difference between lower and higher FBS groups was not significant.

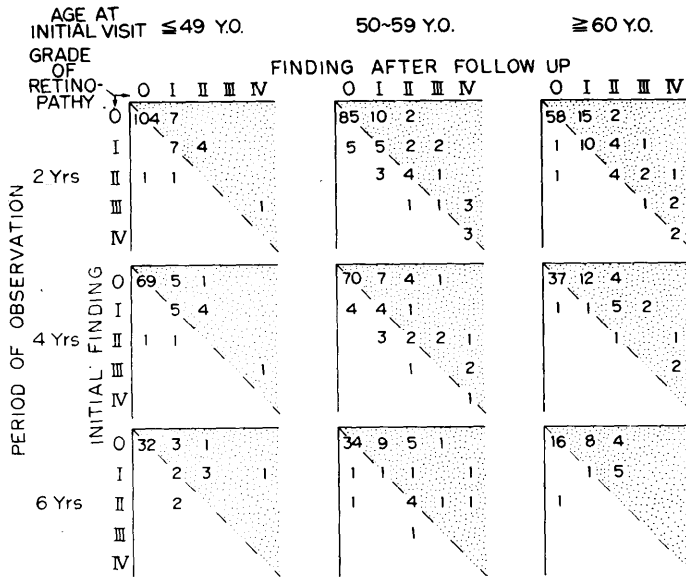


FIG. 7. Follow-up of retinopathy in different age groups. This figure is similar to figure 3 comparing the initial with the follow-up findings in different age groups.

In order to avoid the criticism that the good control group might be predominantly milder cases, while the fair or poor control group might be made up of only severe cases, the following analysis was performed. The good control group and the fair plus poor control group were each divided into two groups based on their initial FBS below and above 170 mg./100 ml. When good control was maintained, the frequency of progression of retinopathy was about the same in the two groups whether the initial FBS was lower or higher than 170 mg./100 ml. (figures 5 and 6). When good control was not achieved, the frequency of progression appeared slightly higher in

the group with higher initial FBS. The difference was not significant statistically, however.

3. Relationship of age with progression of retinopathy

In this series, the occurrence of new lesion in patients under forty-nine years of age was infrequent (figures 7 and 8). Progression was significantly more common in older age groups, particularly because new lesions appeared more often. The differences among these three age groups were significant after 2, 4 and 6 years by the chi square test ($p < 0.01$, < 0.01 and < 0.02 respectively).

4. Comparison of different therapeutic agents

Progression of retinopathy in groups treated with

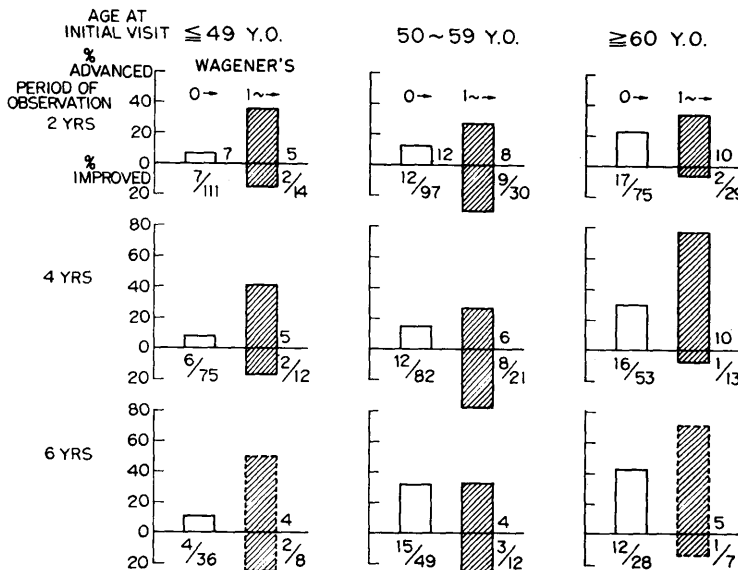


FIG. 8. Difference of progression of retinopathy among different age groups. Derived from figure 7, occurrence of new lesion (white bar) was infrequent under forty-nine years of age and significantly more common in older age groups after 2, 4 and 6 years.

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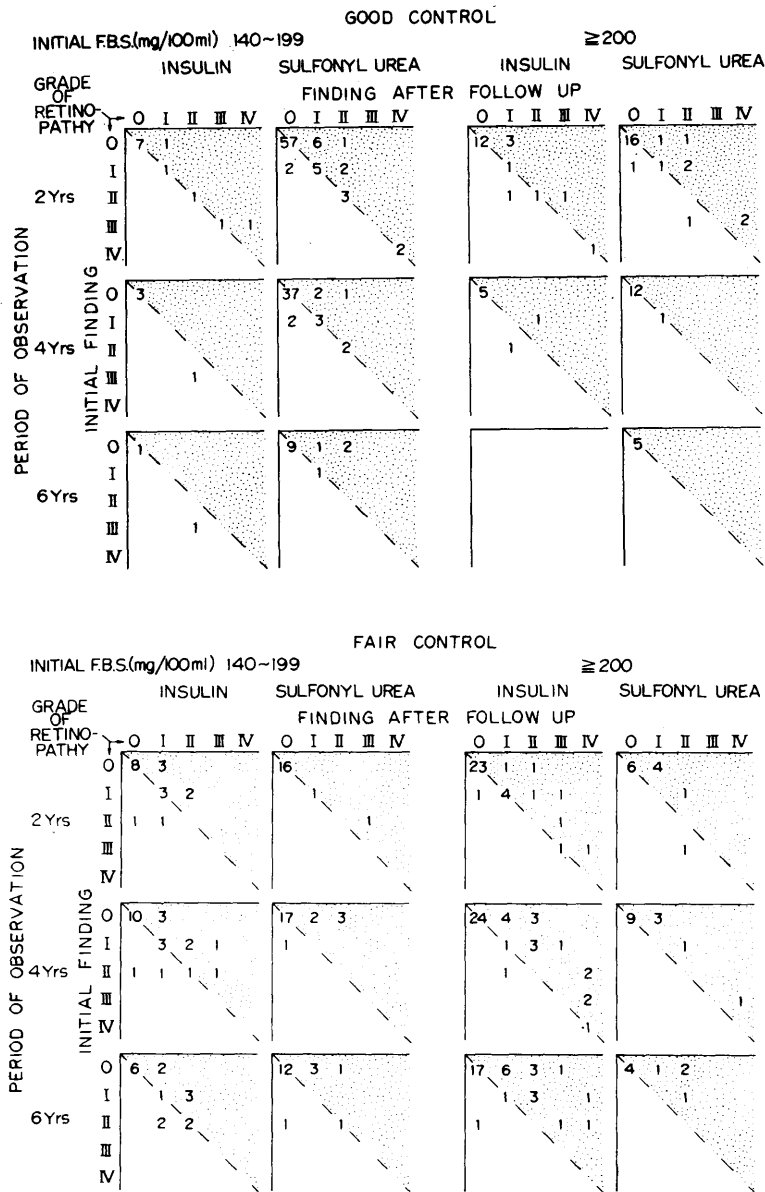


FIG. 9. Progression of retinopathy in patients treated with insulin or sulfonylurea. This figure is similar to figure 3 comparing initial and follow-up findings of patients with similar initial fasting blood sugar who achieved similar degree of control by either treatment. Upper and lower part represents patients who attained good and fair control respectively.

insulin or sulfonylurea was compared in patients who had similar degrees of severity at the initial visit and who achieved the similar degrees of control by either treatment. For this purpose, patients with FBS less than 140 mg./100 ml., for the most part those on sulfonylureas, and patients who failed to achieve good or fair control, for the most part those on insulin, were omitted from the comparison of progression of retinopathy (figure 9). In both good and fair control groups and in groups with initial FBS below and above 200 mg./100 ml., the progression of retinopathy was not more frequent in the sulfonylurea groups than in insulin groups (figure 10).

DISCUSSION

There have been conflicting reports on the effect of control of diabetes on diabetic vascular complications. Regarding diabetic retinopathy, there has been unanimous agreement among different authors however, that the incidence and degree of retinopathy is higher when the duration of diabetes is longer. A large body of evidence suggests that good control of diabetes may delay the course of retinopathy.²⁻⁹ Recently it was demonstrated by the use of fluorescein injection technic that reversal of abnormal retinal finding in a case of juvenile diabetes followed good control of several months.¹⁰ However, whether good control means milder

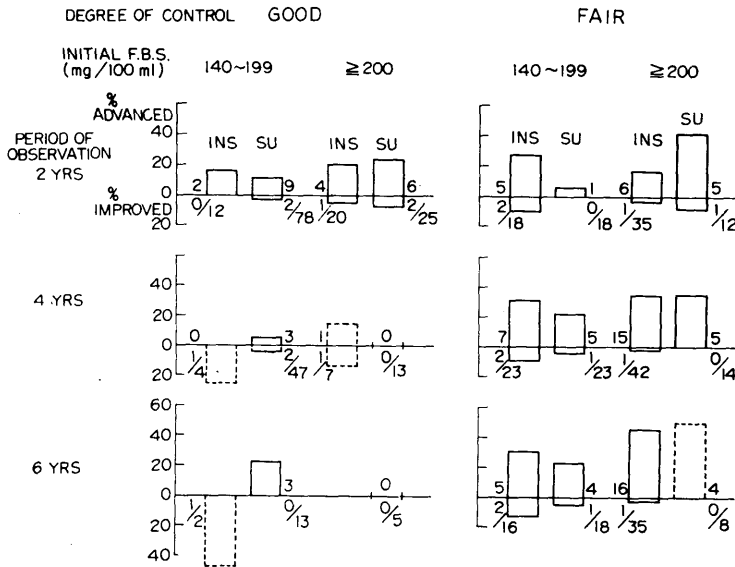


FIG. 10. Comparison of insulin and sulfonylurea therapy concerning progression of retinopathy. Derived from figure 9, each bar represents frequency of progression or improvement of retinopathy. As paired in each group, comparing patients with similar initial fasting blood sugar who achieved similar degree of control on either treatment, progression of retinopathy was not more frequent in sulfonylurea group than in insulin group.

diabetes by nature or result of more strict effort has not been clear.¹¹ The view that progression of diabetic retinopathy is inherent to the severity of diabetes itself rather than to the degree of efforts made for the control of diabetes¹²⁻¹⁶ also warrants careful evaluation, in view of recent reports of specific diabetic complications in patients without overt diabetes.^{18,19}

The present investigation has been directed mainly towards the identification of relationships of severity and control of diabetes with progression of retinopathy. Evaluation of degree of long-term control of diabetes has been considered difficult,¹⁴⁻²⁰ probably because most clinics judge the degree of control by the reports of urine sugar tested by patients themselves, which might be quite unreliable. Therefore, we have adopted FBS determined frequently and regularly as a more objective index as the criterion of long-term control of diabetes.

Our data at the initial visit showed that both the incidence and severity of retinopathy were higher when the duration of diabetes was longer, in agreement with most reports. Moreover, the incidence and severity of retinopathy tended to increase in groups with higher pretreatment fasting blood sugar.

The over-all results suggest that progression of retinopathy may occur more frequently when the control of diabetes is poorer. When control was good, progression was infrequent even in the group with FBS over 170 mg./100 ml. These findings seem to suggest also that the maintenance of good control is more important than the severity of diabetes as judged by the initial FBS, especially in relation to progression of pre-

existing retinopathy. The higher incidence of retinopathy among those with higher blood sugar levels and longer duration at the initial visit (figure 1) might be interpreted also as evidence that the retinal lesion is influenced by the presence of more marked metabolic abnormality for a longer period, and that the fasting blood sugar level is a valid indicator of severity at least of a group.

It must be noted, however, that the period of observation in this study was shorter than those in other reports. Furthermore, the number of juvenile cases was small. The relatively low incidence of very severe retinopathy in our series might be related to these factors. Nevertheless, this period of observation enabled us to relate the degree of control and progression of retinopathy, presumably because of frequent measurement of blood sugar and of objective funduscopic examinations. Significantly lower incidence of progression was observed in patients with good control already after two years of observation. This has encouraged us to continue the study in prospective fashion on an expanded scale.

It is difficult to make a fair comparison of the effects of insulin and oral drugs, firstly because the patients with higher initial FBS are more often treated with insulin from the beginning, thus making the two groups dissimilar, and secondly because those who are not controlled on oral drugs may be changed to insulin thereby making the result of insulin poorer. However, as long as good control was obtained, the use of sulfonylureas did not appear to cause results inferior to those of insulin regarding the course of retinopathy in the

groups with fasting blood sugar between 140 and 199 mg./100 ml. and over 200 mg./100 ml. A more detailed critical prospective study will be required to draw a definite conclusion, however.

In Japan, cerebral vascular disease is a more frequent cause of mortality²¹ than coronary atherosclerosis,²² as compared with Western countries. Juvenile diabetes and cases requiring large doses of insulin are infrequent. The age distribution of the patients followed-up in this study is not unlike that seen in Western clinics except that the juvenile cases were few. The incidence of retinopathy in this series is not very different from that in Western countries despite the lower incidences of myocardial infarction (6/364) and gangrene (0/364) in this series. This may indicate that retinopathy is a more specific complication of diabetes. It is hoped that future investigations on a more expanded scale and in more detail will contribute to the elucidation of pathogenesis of vascular complications of diabetes mellitus.

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