Comparison of Stereofundus Photographs in Patients with Insulin-dependent Diabetes During Conventional Insulin Treatment or Continuous Subcutaneous Insulin Infusion

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SUMMARY

Sixty-five patients with mild to moderate nonproliferative diabetic retinopathy who enrolled in a prospective controlled clinical trial had stereofundus photographs assessed for change over an 8-mo period. The entire study group showed a worsening of retinopathy with time ($P < 0.001$). The worsening was greater in the pump-treated group (15/32) than in the conventionally treated group (9/33). The significance of this difference ranged from $P = 0.67$, if changes in *mean* retinopathy level for each patient were compared, to $P = 0.177$ if a grading system keyed to the worse eye was compared. The difference in rates of change between treatment groups was found to be related to the baseline *mean* retinopathy level ($P = 0.031$), but less significantly so if baseline retinopathy keyed to the worse eye was used as a covariate ($P = 0.08$). Worsening occurred more frequently in those patients starting with the lower retinopathy levels.

Progression was associated with the appearance of retinal infarcts (cotton-wool spots, soft exudates) and/or intraretinal microvascular abnormalities, with the pump patients showing a significant increase in these individual retinal lesions compared with the conventionally treated patients over 8 mo ($P < 0.025$).

DIABETES 1985; 34 (Suppl. 3):50–55.

The goal of management of diabetes mellitus is often near-normalization of glycemia, the belief being that "tight" control of plasma glucose levels will lessen the incidence and/or severity of microangiopathy and thus diabetic retinopathy. This article will deal with the results of the analysis of stereofundus photographs taken at baseline (0 mo) and 8 mo in the prospective, randomized, multicentered clinical trial of conventional insulin treatment (CIT) or continuous subcutaneous insulin infusion (CSII) known as the Kroc Collaborative Study.

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METHODS

Patients recruited at each of the six clinical centers of the Kroc Collaborative Study Group were randomized to CIT or CSII (see article by Champion et al., pages 5–12, this supplement). Stereoscopic pairs of eight standard 30° photographic fields were taken of each eye at baseline (0 mo) and again at the 8-mo follow-up visit. Each completed "photo set" was forwarded to the Fundus Photograph Reading Center at the University of Wisconsin. There, retinopathy severity in each photo set was graded according to a classification scheme specifying seven overall "retinopathy levels" and explained in detail in the article by Davis et al., pages 42–49, this supplement. The classification system is based on the Modified Airlie House Classification[1] as adapted for the Early Treatment Diabetic Retinopathy Study (ETDRS),[2] and just recently published[3] (Table 1).

Graders were masked with respect to patient identity, photo set sequence, clinic, eye photographed, and treatment group. Results of the grading process were entered into a computer to allow collation and sorting. Retinopathy levels were assigned to each eye and, in addition, patient retinopathy levels were determined (1) by linking the levels of the two eyes but keying in on the worse eye, thus creating a 13-step "worse eye emphasized" patient retinopathy scale (Table 2),[3] which is essentially the same as the 11-step scale recently applied to these data,[4] and (2) by simply taking the mean of the retinopathy level of the two eyes ("mean retinopathy" level). Severity of individual lesions was also assessed.

For levels determined by the "worse eye emphasized" method, change in patient level between baseline and the 8-mo visit was determined using a five-step scale where 1 = improved 2 or more levels, 2 = improved 1 level, 3 = no change, 4 = worsened 1 level, and 5 = worsened 2 or more levels. For levels determined by the "mean retinopathy" level method, change in patient level between baseline and the

TABLE 1
Definitions of retinopathy levels

Level 10	No retinopathy
Level 20	Microaneurysms (1 or more) only
Level 30	Microaneurysms and 1 or more of the following: Retinal hemorrhage (H/Ma) <standard photo #2A Hard exudates (HE) <standard photo #3 Retinal infarcts (soft exudates, SE) questionably present Intraretinal microvascular abnormalities (IRMA) questionably present Venous beading (VB) questionably present Venous loops definitely present
Level 40	Microaneurysms and 1 or more of the following: H/Ma ≥standard photo #2A HE ≥standard photo #3 Retinal infarcts (soft exudates, SE) definitely present IRMA definitely present VB definitely present
Level 50	In fields 4–7 only either: At least 3 of the following: H/Ma ≥standard photo #2A in 1 field or more Retinal infarcts (soft exudates, SE) definitely present in at least 2 fields IRMA definitely present in at least 2 fields VB definitely present in at least 2 fields or IRMA present in 4 fields and ≥standard photo #8A in at least 2 fields
Level 65	New vessels and/or fibrous proliferations within 1 disc diameter of the disc (NVD, FPD) or elsewhere (NVE, FPE) or preretinal and/or vitreous hemorrhage, but not Diabetic Retinopathy Study (DRS) "high risk characteristics"
Level 70	DRS high risk characteristics[11]

8-mo visit was determined by subtracting the 0-mo from the 8-mo value in each case.

Change scores were then generated allowing comparisons to be made between treatment groups with respect to the progression of retinopathy, to change as a function of the baseline retinopathy level, and to change as a function of the right or left eye and the better or worse eye at baseline. Patient retinopathy levels and change in retinopathy levels are presented in two different ways: the "worse eye emphasized" method, which stresses the worse eye but does not ignore the better eye, and the "mean retinopathy" method, which represents a straightforward averaging of the retinopathy level in each eye. The former method is preferred by the Fundus Photograph Reading Center because it is more consistent with clinical practice (see article by Davis et al., pages 42–49, this supplement).

Changes in individual lesions were based on lesion change scores assigned, using a multistep scale, where −4 = improved 4 grades, −3 = improved 3 grades, −2 = improved 2 grades, −1 = improved 1 grade, 0 = no change, +1 = worsened 1 grade, +2 = worsened 2 grades, +3 = worsened 3 grades, and +4 = worsened 4 grades. A detailed description of the grading method for each lesion is beyond the scope of this article but has been previously published.[1]

Statistical analysis was performed using analysis of variance (ANOVA) and in the case of nonparametric data, using the Wilcoxon sign rank and Mann-Whitney tests.[5] The chi square test was used to evaluate the effect of treatments on lesion grades.[6]

TABLE 2
Patient retinopathy levels at baseline (0 mo) using "worse eye emphasized" grading method

Retinopathy level	Treatment group: CSII N (%)	Treatment group: CIT N (%)
10 = 10	1 (3.0)	1 (3.0)
20 < 20	0 (0.0)	1 (3.0)
20 = 20	1 (3.0)	6 (18.2)
30 < 30	4 (12.1)	4 (12.1)
30 = 30	3 (9.1)	1 (3.0)
40 < 40	8 (24.0)	7 (21.2)
40 = 40	14 (42.4)	11 (33.3)
50 < 50	0 (0.0)	0 (0.0)
50 = 50	0 (0.0)	0 (0.0)
65 < 65	1 (3.0)	2 (6.1)
65 = 65	1 (3.0)	0 (0.0)
Total	33 (100)	33 (100)

CSII = continuous subcutaneous insulin infusion; CIT = conventional insulin treatment.
N(%) = number of patients (% of total treatment group).

RESULTS

Of the 70 patients randomized, 68 patients completed the study. Three patients (one in the CIT group and two in the CSII group) had missing photo sets either at baseline or the 8-mo visit, and progression could not be assessed. These data were therefore excluded from the analysis of change in retinopathy level over the 8-mo period.

Table 2 presents the baseline distribution of patient retinopathy levels in each treatment group based on the "worse eye emphasized" method of grading. In each group, three patients did not meet the ophthalmologic baseline eligibility requirements but were included in later change scores. Each treatment group at baseline included one patient with no retinopathy and two patients with proliferative retinopathy. As prescribed by the protocol, the majority of patients in each treatment group had mild to moderate nonproliferative retinopathy at baseline. The apparent preponderance of very mild nonproliferative diabetic retinopathy characterized by

TABLE 3
Patient retinopathy levels at baseline (0 mo) using "mean retinopathy"* grading method

Mean retinopathy level	Treatment group: CSII N (%)	Treatment group: CIT N (%)
10.00	1 (3.0)	1 (3.0)
15.00	0 (0.0)	1 (3.0)
20.00	1 (3.0)	6 (18.2)
25.00	5 (15.2)	4 (12.1)
30.00	6 (18.2)	5 (15.2)
35.00	4 (12.1)	3 (9.1)
40.00	14 (42.4)	11 (33.3)
52.50	1 (3.0)	2 (6.1)
65.00	1 (3.0)	0 (0.0)
Total	33 (100)	33 (100)

Definitions of retinopathy levels and abbreviations are found in Table 1.
*Average of the retinopathy level for each eye.

TABLE 4
Patient retinopathy levels at 8 mo using "worse eye emphasized" grading method

Retinopathy level	Treatment group CSII N (%)	CIT N (%)
10 = 10	1 (3.0)	1 (2.9)
20 < 20	0 (0.0)	1 (2.9)
20 = 20	1 (3.0)	2 (5.9)
30 < 30	0 (0.0)	7 (20.6)
30 = 30	2 (6.1)	0 (0.0)
40 < 40	5 (15.2)	8 (23.5)
40 = 40	19 (57.6)	11 (32.4)
50 < 50	1 (3.0)	1 (2.9)
50 = 50	0 (0.0)	0 (0.0)
65 < 65	2 (6.1)	3 (8.8)
65 = 65	2 (6.1)	0 (0.0)
Total	33 (100)	34 (100)

Definitions of retinopathy levels and abbreviations are found in Table 1.

microaneurysms (Ma) only in the CIT group was not statistically significant (P = 0.5, chi square). Similar insignificant differences between the treatment groups at baseline were obtained using the "mean retinopathy" grading method (Table 3).

There were no differences between treatment groups at baseline or during the course of the study with respect to the results of the ophthalmologic examination (see article by Champion et al., pages 5–12, this supplement) other than in the fundus photographs and the fluorescein angiograms (see article by Kohner et al., pages 56–60, this supplement). Table 4 presents the 8-mo visit distribution of patient retinopathy levels based on the "worse eye emphasized" method of grading fundus photographs. Table 5 presents the same data with levels assigned according to the "mean retinopathy" method of grading.

Table 6 documents the change in patient retinopathy levels over the 8-mo study period by treatment group. Baseline and 8-mo comparisons could be made in only 65 patients. Both treatment groups showed a predominant tendency to remain unchanged: 18 (56%) in the CSII group and 22 (67%) in the CIT group. One patient (3%) in the CSII group and 2 patients (6%) in the CIT group improved 1 retinopathy level with the remainder worsening over the study period: 7 (22%) CSII and 7 (21%) CIT worsened by 1 level with 6 (19%) CSII and 2 (6%) CIT worsening by 2 or more retinopathy levels. The overall worsening with time for the entire study population was highly significant, whether analyzed by parametric (P < 0.0001) or nonparametric (P < 0.0002) techniques.

The rate of worsening when using the "worse eye emphasized" technique of grading was greater in the CSII group than in the CIT group, but the difference is not statistically significant (P = 0.156 ANOVA and P = 0.177 Mann-Whitney). If the baseline retinopathy level is used as a covariate, the difference between treatment groups is more obvious but still does not reach statistical significance (P = 0.08). There was a greater tendency for those patients with milder retinopathy at baseline to progress when compared with those patients with moderate or severe nonproliferative retinopathy, but the number of patients in each group is not large enough for meaningful statistical analysis. If the "mean retinopathy" method of grading is used, the difference in the rate of worsening between the treatment groups is still below conventional levels of statistical significance (P = 0.067) by either parametric or nonparametric tests. However, with baseline mean retinopathy level as a covariate, the difference in rates of progression between treatment groups is statistically significant (P = 0.031).

Table 7 presents the number of patients, in specific groupings of retinopathy level at baseline using the "worse eye emphasized" system, that progressed one or more retinopathy levels and the change in the lesion or lesions responsible for that progression. Progression was most commonly due to the appearance of retinal infarcts (soft exudates, cotton-wool spots) and/or intraretinal microvascular abnormalities.

Analysis was undertaken to determine whether assessment of the worse eye only or the best eye only from 0–8 mo was a confounder with respect to progression of disease, and no significant difference was found. Similarly, assessing the right eye or the left eye only had no effect on the degree of change in retinopathy levels.

Individual lesions comprising nonproliferative diabetic retinopathy were graded, and change in grade was determined for each patient over the 8-mo study period, according to treatment group. Table 8 documents the change in grade for each lesion within each treatment group and the statistical significance (if any) of the difference of that change between treatment groups. Lesions studied include hemorrhages/microaneurysms (H/Ma), hard exudates (HE), soft exudates (SE, retinal infarcts, cotton-wool spots), venous beading (VB), venous loops and reduplication (VLR), intraretinal microvascular abnormalities (IRMA), neovascularization of the disc (NVD), neovascularization elsewhere (NVE), fibrous proliferation (FP), and preretinal/vitreous hemorrhage (PRVH). The CSII group showed a statistically significant increase in SE and IRMA when compared with the CIT group using the two-way chi square (P = 0.025). The remaining lesions showed no change between treatment groups.

DISCUSSION

One of the goals of the Kroc Collaborative Study Group was to assess quantitative methods for evaluating changes in diabetic retinopathy with time. The methods used to evaluate

TABLE 5
Patient retinopathy levels at 8 mo using "mean retinopathy"* grading method

Mean retinopathy level	Treatment group CSII N (%)	CIT N (%)
10.00	1 (3.0)	1 (2.9)
15.00	0 (0.0)	1 (2.9)
20.00	1 (3.0)	2 (5.9)
25.00	0 (0.0)	7 (20.6)
30.00	4 (12.1)	4 (11.8)
35.00	3 (9.1)	4 (11.8)
40.00	19 (57.6)	11 (32.4)
45.00	1 (3.0)	1 (2.9)
52.50	2 (6.1)	3 (8.8)
65.00	2 (6.1)	0 (0.0)
Total	33 (100)	34 (100)

Definitions of retinopathy levels and abbreviations are found in Table 1.
*Average of the retinopathy level for each eye.

TABLE 6
Change in patient retinopathy level (0–8 mo) using (1) "worse eye emphasized" grading method and (2) "mean retinopathy level" grading method

Change score	Treatment group CSII N (%)	CIT N (%)
(1) "Worse eye emphasized" grading method		
2	1 (3.1)	2 (6.1)
3*	18 (56.3)	22 (66.7)
4	7 (21.9)	7 (21.2)
5	6 (18.2)	2 (6.1)
Total	32 (100)	33 (100)
(2) "Mean retinopathy level" grading method		
−5.00	1 (3.1)	3 (9.1)
0.00*	16 (50.0)	21 (63.7)
+5.00	8 (25.0)	6 (18.2)
10.00	4 (12.5)	1 (3.0)
12.50	0 (0.0)	1 (3.0)
15.00	2 (6.3)	1 (3.0)
25.00	1 (3.1)	0 (0.0)
Total	32 (100)	33 (100)

Definitions of retinopathy levels and abbreviations are found in Table 1.
*Score for "no change" observed.

the stereofundus photographs have been explained in detail (see article by Davis et al., pages 42–49, this supplement). It is clear from our results that near-normalization of mean plasma glucose achieved during treatment with CSII in patients with mild to moderate nonproliferative diabetic retinopathy does not prevent progression of retinopathy over an 8-mo period. Furthermore, there appears to be a definite trend to greater worsening of mild to moderate retinopathy in those patients treated with CSII as compared with those treated with CIT. The worsening in retinopathy levels appears to result primarily from the development of SE and/or IRMA. The rate of progression over 8 mo of our CSII group (40.6% progression of one or more levels and 18.8% of two or more levels) may well be more rapid than the rate of progression over 2 yr for conventionally treated diabetic patients (41.2% one or more levels, 19.2% two or more levels) recently published by Klein et al.[3] The rate of progression of our CIT group at 8 mo (27.3% one or more levels and 6.1% two or more levels) is, as one might expect, comparable by extrapolation to these published 2-yr rates.

Our results are consistent with the published findings of the Steno Study Group[7] and lend support to the clinical impression held by many endocrinologists and ophthalmologists that rapid regulation of blood glucose can lead to a worsening of retinopathy in some patients.[8] The exact cause of this apparent worsening is unknown; it appears to be associated with signs of capillary nonperfusion and consequent hypoxia (retinal infarcts and IRMA), and there has been speculation that a reduction in retinal perfusion as well as nutrient substrate levels could account for an increase in retinal infarcts. Whether there is a relationship between development of retinal infarcts and subclinical or symptomatic hypoglycemia remains uncertain (see article by Testa et al., pages 61–68, this supplement).

The results of this controlled clinical trial must be placed in proper context. The apparent worsening of the level of retinopathy in the CSII group relative to patients treated conventionally is indicated by the assessments of both color fundus photographs and fluorescein angiograms (see article by Kohner et al., pages 56–60, this supplement) but, like the findings of the Steno Study Group,[7] was not associated with changes in visual acuity. Unlike the subjects of Steno Study Group, our patients entered the trial with very mild to moderate nonproliferative diabetic retinopathy. The degree of retinopathy in the Steno patients, more advanced nonproliferative or proliferative diabetic retinopathy (see article by Lauritzen et al., pages 74–79, this supplement), was more closely comparable with that in previously published reports documenting the failure of CSII to halt progression of advanced nonproliferative or proliferative diabetic retinopathy.[9,10] The Kroc Study extends this finding to encompass patients with mild diabetic retinopathy treated with CSII for 8 mo.

It would be an incorrect assumption to state that CSII causes a worsening of mild established diabetic retinopathy; both the CSII and the CIT groups worsened during the study period, albeit at different rates. Our results could simply be

TABLE 7
Reasons for progression of diabetic retinopathy using "worse eye emphasized" grading method

Level of retinopathy	Treatment group	Total number	Number progressing	Reason for progression
20 = 20 or better	CSII	2	0	
	CIT	8	4	H(2), HE(2)
30 < 30 to 30 = 30	CSII	7	7	HE(1), SE(1) SE + IRMA(4), IRMA(1)
	CIT	5	2	HE(1), SE(1)
40 < 40 to 40 = 40	CSII	21	6	IRMA(1), SE(1), SE + IRMA(3), PDR(1)
	CIT	18	3	IRMA(1), IRMA + SE(1), PDR(1)
50 < 50 to 65 = 65	CSII	2	0	
	CIT	2	0	
Total	CSII	32	13	(41%)
	CIT	33	9	(27%)

Abbreviations as in Tables 1 and 2.

TABLE 8
Change in lesion grades (0–8 mo) by treatment group

Treatment	Lesion change score*							Total
Hemorrhages/microaneurysms	−1	0	1	4				
CIT	6 (9.4)	48 (75)	10 (15.6)	0 (0.0)				64
CSII	6 (9.1)	48 (72)	11 (16.7)	1 (1.5)				66
	P = 0.797							
Hard exudates	−3	−2	−1	0	1	2	3	
CIT	0 (0.0)	3 (4.7)	8 (12.5)	36 (56.3)	9 (14.1)	6 (9.4)	2 (3.1)	64
CSII	1 (1.5)	4 (6.1)	7 (10.6)	33 (50.0)	6 (9.1)	14 (21.2)	1 (1.5)	66
	P = 0.488							
Retinal infarcts (soft exudates)	−2	−1	0	1	2	3		
CIT	3 (4.7)	4 (6.3)	44 (68.8)	7 (10.9)	6 (9.4)	0 (0.0)		64
CSII	4 (4.5)	7 (10.6)	28 (42.4)	13 (19.7)	14 (21.2)	1 (1.5)		66
	P = 0.066							
Venous beading	−3	−2	−1	0	1	2	3	
CIT	1 (1.6)	1 (1.6)	0 (0.0)	59 (92.2)	3 (4.7)	0 (0.0)	0 (0.0)	64
CSII	0 (0.0)	1 (1.5)	2 (3.0)	54 (81.8)	7 (10.6)	1 (1.5)	1 (1.5)	66
	P = 0.341							
Venous loops–reduplication	−2	−1	0	1	2			
CIT	2 (3.1)	4 (6.3)	54 (84.4)	2 (3.1)	2 (3.1)			64
CSII	3 (4.5)	6 (9.1)	47 (71.2)	10 (15.2)	0 (0.0)			66
	P = 0.078							
Intraretinal microvascular abnormalities	−2	−1	0	1	2	3		
CIT	2 (3.1)	2 (3.1)	47 (73.4)	8 (12.5)	2 (3.1)	3 (4.7)		64
CSII	2 (3.0)	5 (7.6)	32 (48.5)	18 (27.3)	8 (12.1)	1 (1.5)		66
	P = 0.028							
Neovascularization of the disc	−1	0	2	3				
CIT	1 (1.6)	63 (98.4)	0 (0.0)	0 (0.0)				64
CSII	0 (0.0)	63 (95.5)	2 (3.0)	1 (1.5)				66
	P = 0.265							
Neovascularization elsewhere	0	1	2					
CIT	62 (96.9)	1 (1.6)	1 (1.6)					64
CSII	62 (93.9)	3 (4.5)	1 (1.5)					66
	P = 0.616							
Fibrous proliferations	0	1	2					
CIT	64 (100)	0 (0.0)	0 (0.0)					64
CSII	64 (97.0)	1 (1.5)	1 (1.5)					66
	P = 0.374							
Preretinal and vitreous hemorrhage	0							
CIT	64 (100)							64
CSII	66 (100)							66
	P = nil							

Abbreviations as in Table 1.
*As described in METHODS.

a documentation of the "natural" fluctuation of the various lesions comprising diabetic retinopathy. Much longer trials are necessary, having as their end point clinically meaningful progression of retinopathy, such as the development of "high risk characteristics" as documented by the Diabetic Retinopathy Study.[11]

The Kroc Collaborative Study Group has provided preliminary evidence suggesting that CSII does not prevent progression of mild nonproliferative diabetic retinopathy. The need is clear for a long-term controlled clinical trial of the efficacy of CSII and the necessity to include a prevention group within such a larger and longer study. A format for the

assessment of the several grading methods of diabetic retinopathy has been developed by the Fundus Photograph Reading Center at the University of Wisconsin. The torch is passed to the Diabetes Control and Complications Trial[12] to illuminate the path leading to the eventual elimination of diabetic microangiopathy.

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