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ABSTRACT. Continuous subcutaneous insulin administration (CSII) is known to provide a better glucose control than conventional insulin treatment (CIT). Early anecdotal reports claimed that diabetic retinopathy could be dramatically reversed by CSII treatment. More prolonged studies were however less enthusiastic: only slightly better retinal outcome was observed in those diabetic patients in CSII regimen. The aim of the present study was to investigate the mid-term effects of CSII, as compared with conventional treatment, on the evolution of the ischaemic retinal changes in a group of diabetic subjects. A multicentre prospective study was designed by the Italian CNR and carried out by the Universities of Padua, Milan, Perugia and the Fidia Research Laboratories. Thirty-eight Type I insulin-dependent diabetic patients were blindly assigned by paired randomization to CSII or CIT after matching for sex, age, duration of diabetes and retinal status. To assess the evolution of retinopathy, fluoroangiographic changes of ischaemic areas were blindly evaluated and reported as improved, stable and worsened. The degree of ischaemia was also scored by means of a quantitative method (Dokumator). At the baseline metabolic parameters were not statistically different between the two treatment groups. After 24 mo, CSII patients reached a better glycaemic control than those treated by CIT (daily glucose profile, glycosylated haemoglobin were significantly lower in the CSII group). While qualitative evaluation of retinal changes showed a slightly but not significantly better outcome in the CSII patients, quantitative assessment demonstrated a significantly lower deterioration in the CSII group. Furthermore, an evident correlation was observed between systolic blood pressure and retinal deterioration. In conclusion, our results support the point of view that, even though CSII does not prevent the development of proliferative retinopathy, the deterioration of retinal microangiopathy, even at a relatively advanced stage such as ischaemic retinopathy, could be retarded by strict metabolic control achieved by CSII.

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INTRODUCTION

Conventional insulin therapy (CIT) in diabetic patients fails to restore the finely regulated glucose homeostasis of normal subjects (1). On the other hand, the suggestion that microvascular complications of diabetic patients are in part due to the lack of good blood glucose (BG) control, has prompted the introduction of home BG monitoring and intensified insulin treatment, in the attempt to achieve normoglycaemia. Open-loop devices, where the feed-back control is eliminated and continuous subcutaneous insulin administration (CSII) is preprogrammed according to predetermined insulin requirements, appear to provide better glucose control than usual conventional treatment (2, 3). Early anecdotal reports claimed that CSII dramatically improved diabetic control as well as diabetic retinopathy (4, 5). However, the results of more prolonged studies were less enthusiastic showing only a slightly better outcome for retinopathy in the CSII treated patients (6) or even worsening of retinopathy after short-term strict tightening of metabolic control (7, 8). With regard to these apparently paradoxical findings, it has been hypothesized that it is not the intensified insulin treatment itself but the relatively abrupt lowering of BG which plays a major role in worsening the retinal status (9). Recently, more encouraging results have been reported by long-term studies which have shown that two years of near-normoglycaemia can positively interfere with the progression of diabetic microangiopathy in the retina and in the kidney (9).

More recent reports on long-term studies fail to demonstrate a statistically significant benefit of the improvement of glycaemic control on the evolution of diabetic retinopathy even though a tendency to retarded progression of retinal lesions was observed in patients with intensified insulin regimens (10).

The aim of the present study was to investigate by means of qualitative and quantitative methods (11) the effects of CSII as compared to CIT in the retinal outcome of a group of diabetic subjects characterized by retinopathy with mild to discrete ischaemic areas but without any sign of preproliferative or proliferative changes. The rationale of this study was to evaluate whether the attempt to achieve strict metabolic control in patients showing a rather advanced deterioration of the retina, avoiding at the same time too rapid reduction of BG levels, could play a favourable role in the progression of retinal microangiopathy.

MATERIALS AND METHODS

The criteria for the selection of the patients in the three centres participating in the study (Padua, Milan and Perugia) were as follows: 1) C-peptide peak following glucagon challenge < 0.2 μmol/ml; 2) serum creatinine $< 150/$μmol/ml; 3) albumin excretion rate < 1 gr/day; 4) systolic blood pressure < 160 mmHg; 5) diastolic blood pressure < 95 mmHg; 6) ideal body weight within 90 and 120% range according to the Metropolitan Life Insurance Co. Tables (Chicago, 1959); 7) age between 18 and 55 yr; 8) duration of diabetes > 5 yr; 9) background diabetic retinopathy with areas of capillary non-perfusion; 10) absence of somatic denervation neuropathy; 11) absence of symptomatic angina and myocardial infarction; 12) absence of preproliferative or proliferative retinopathy; 13) absence of other concomitant retinal disease; 14) absence of previous retinal laser treatment.

More than 3,000 patients had been screened and 38 were considered eligible for the study (14 in Padua, 12 in Milan and 12 in Perugia).

Once the subjects were matched for sex, age and retinal status, pairs were created and the components were randomly allocated, one to CSII treatment and the other to CIT.

With particular regard to retinopathy, all the patients had mild background diabetic retinopathy with small and not confluent areas of capillary non-perfusion in at least one of 7 standard fields. Those patients who completed a two-year study were considered to have concluded the trial. If proliferative lesions appeared before two years, laser treatment was carried out and this was considered the endpoint of the trial.

Retina evaluation

At baseline and every 6 mo each patient underwent an ophthalmological exam including: refraction with best corrected visual acuity, anterior segment biomicroscopy, registration of intraocular pressure, direct and indirect ophthalmoscopy, colour retinal photography and fluorescein angiography of both eyes. For the colour fundus photography, a 45° angle retina camera with Kodak 64 professional film was used. Pictures were taken on 7 standard

fields (Fig. 1). A 45° angle camera was also used for the fluorescein angiography. After rapid injection of 5 ml of 20% sodium fluorescein in an antecubital vein, pictures were taken on the 7 standard fields (Fig. 1) including the posterior pole (field 1), mid-periphery (field 2, 3 and 4) and periphery (field 5, 6 and 7). Early phases (arterial, arteriovenous and venous phases) were taken on field 1; late phases (7 minutes after the injection of the dye) on field 1 and 2. Both eyes were separately submitted to angiography, at a distance of at least 24 hr and no more than 72 hr. The film used for the angiography (Kodak Tri-X PAN, 400 ASA) was processed in Kodak D-76 developer (at 20° C for 11 min with continuous mixing) and fixed on Refinal. Fluorescein angiograms of the baseline and those obtained after 2 yr were considered for the comparison. Those patients who developed proliferative lesions during the study were treated with laser photocoagulation and considered to have concluded the trial. If laser treatment was applied after entering the study, the last angiogram before photocoagulation was used for comparison with that of the baseline.

According to the purpose of this study, only changes of ischaemic areas and appearance of new vessels were taken into consideration. For the analysis of the retinal outcome, qualitative and quantitative methods were applied separately.

1) *Qualitative method:* fluorescein angiographies were blindly and independently assessed by three groups of readers, each group comprising three ophthalmologists. Each of the 7 standard fields of fluorescein angiography at the baseline were compared with the same field obtained at the end of the study. No observer could know which of the angiographies was that of the baseline or that of the endpoint. A cumulative judgement regarding the variation of the ischaemic areas for each eye was given. Whenever disagreements among the three groups of observers were apparent, a joint but blind evaluation was given. The results were reported for each patient as improved, stable or worsened. Significant changes in the extension of ischaemic areas were considered signs of deterioration, or improvement. Patients were considered worsened when at least one eye appeared deteriorated, and improved when at least one eye ameliorated. In only one patient one eye showed worsening and the other improved; the final judgement,

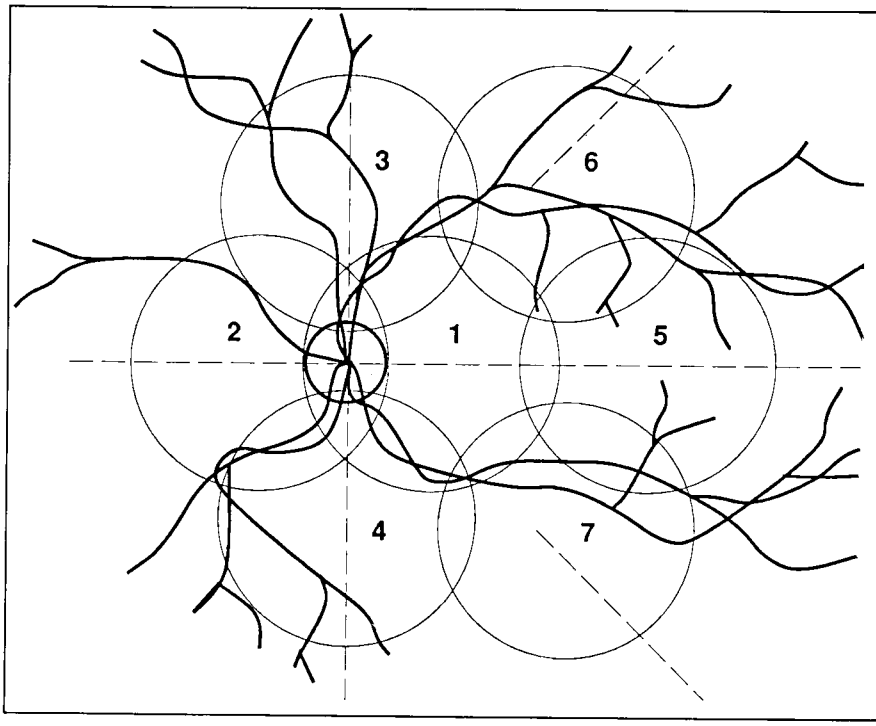

Fig. 1 - *The drawing schematically shows the 7 standard fields chosen for the fundus photography and for fluorescein angiography. Field 1 represents the posterior pole, the margin of the field touches the nasal edge of the disc; field 2 takes the nasal area (axis D); field 3 and 4 the retina superior and inferior of the disc, respectively (axis 90 and 270); fields 5, 6 and 7 are tangent to the macular region and accounts for the temporal retina (axis 180, 135 and 225 respectively). Early phases are taken only on field 1, until venous retinal filling is completed, then pictures are taken on the other fields. Late phases are taken on fields 1 and 2, 7 minutes after injection.*

by means of an open evaluation, was given by an external senior ophthalmologist.
2) *Quantitative method:* this method was applied only on field 1 (posterior pole) and 2 (nasal area). The Dokumator (Carl Zeiss, Jena, D.D.R.) was used to obtain sufficient magnification of the negative film of the angiography. On the magnified images of the two fields, ischaemic areas were carefully delimited. By means of a computer image analyzer, the total area of ischaemia was then calculated and reported in arbitrary area units, being 32000 the maximum score for each of the two fields. Eventually, a cumulative score for the individual patient was obtained. Comparison between the basal score and that of the endpoint was then carried out.

Metabolic parameters
The patients selected for the study were followed over a period of 2 yr and the retinal status, as well as the metabolic control, were evaluated at predetermined times. Capillary glucose levels were measured by a reflectance meter (Reflomat, Boehringer, Mannheim, West Germany); by which 7 blood glucose values by finger prick were obtained once a week, using disposable lancets before, and 90 min after, each of the three major meals and before bedtime. Whole venous blood samples were collected once a month, haemolysates were prepared, "pre-HbA_1" was removed by incubation and samples were then assayed using a column anion exchange technique (Biorad Lab., Richmond, USA) (12). Total serum cholesterol, tryglicerides, HDL-cholesterol, azotaemia and creatinine were measured, employing standard techniques (13-15), after an overnight fast. Capillary BG levels were assessed by the patients themselves and recorded monthly during the outpatient clinic visits. An outpatient metabolic control evaluation was also assessed every 2 mo and the following parameters were measured: body mass index (kg/m^2); systolic and diastolic blood pressure (mmHg). The values of 5 controls were considered for the analysis: the baseline, the 6th, 12th, 18th, 24th month of the study.

Statistical methods
All the statistical analyses were conducted with the BMDP Statistical Package (16). The pairing criteria stated by the study protocol, forced all the statistical tests and procedures applied in the analysis to be based on paired samples. This fact also forced the observations to be expressed in terms of differences instead of rough measurement: the value representing the paired observation consists in the difference between the value of the CSII component and the value of the CIT one.
A) *Randomization:* the Student's *t* test, applied to the baseline values of all the parameters observed, was used to assess the randomization procedure that assigned the two treatments within each pair. The Wilcoxon signed rank test was applied to baseline Dokumator readings to assess the comparability of retinal compromission between the paired components before entering the study.
B) *Reliability of retina evaluation:* the agreement between the ophthalmologists of the three Centres in evaluating retinal outcome (qualitative judgement) was measured by means of K-reliability index (17). Taking into consideration data from a previous pilot study, Dokumator reliability was evaluated. Intra-rater reliability was quantified by means of r' intra-class correlation coefficient (18), and inter-rater reliability was measured by means of linear correlation coefficient. Retina relative changes obtained from Dokumator readings were categorized into a three item qualitative score (improved, stable, worsened) according to 99.9% confidence interval estimated on pilot study data. The agreement between qualitative and quantitative evaluations of retinal status was measured and tested by means of Cohen Kw index (19) with weight matrix by Cicchetti.
C) *Follow-up:* the Student's *t* test was applied to the values of the parameters observed at the four steps of the study (6th, 12th, 18th, 24th mo) to verify the hypothesis of a different effect of the two treatments on the metabolic control. The McNemar test (20) to assess the possible correlation between insulin administration mode and retinal outcome (classified by means of qualitative score) was used. For each pair both the absolute change of ischaemic areas (final value minus basal value) and the relative change from the basal value (final value minus basal value out of the basal value) were considered as quantitative measures of retinopathy evolution, over the period 0-24 mo. The hypothesis of treatment influence on the retinal outcome was verified applying the Wilcoxon signed rank test to absolute changes and the Student's *t* test to relative changes.

D) *Multiple linear regression:* stepwise linear regression analyses were carried out to point out any casual relationship between the levels of the metabolic parameters and the retinal outcome. The estimated models considered as dependent variables the absolute change and the relative change of the ischaemic area in each pair. The means of the 5 evaluations of the following parameters were used as independent variables: mean daily BG, systolic blood pressure, diastolic blood pressure, HbA_{1c} and body mass index.

RESULTS

Thirty-eight patients were selected as a whole, each following the inclusion/exclusion criteria listed above. Details about the patients are given in Table 1. The two groups of subjects were well matched with regard to all the clinical parameters taken into consideration, even when pairs were created. Seventeen out of 19 pairs completed the study, while 2 pairs dropped out before the second year control because they did not perform the final 24th month evaluation.

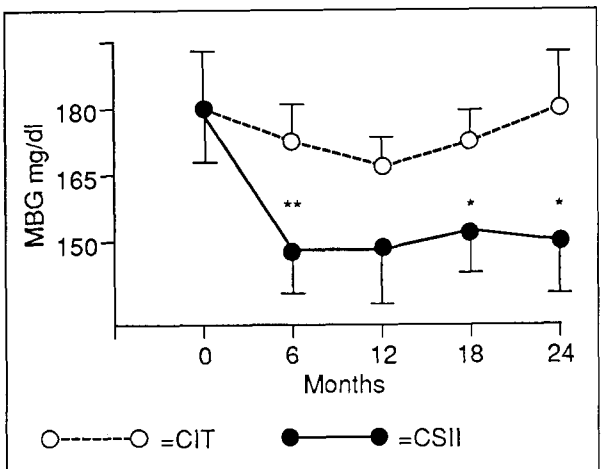

Fig. 2 - *Mean daily blood glucose profile (MBG) of both treatment groups during the study. From statistically not different values at baseline, MBG after endpoint shows a significant better modification in the CSII group. Asterisks denote significant differences between the two treatment groups (paired Student's t test).* *= $p < 0.05$; **= $p < 0.01$.

Table 1 - *Baseline summary of clinical data (mean ± SE, range).*

Parameter	CSII	CIT
Sex and n	M = 10 F = 9	M = 10 F = 9
Age (yr)	36.3 ± 2.10 (23-55)	37.9 ± 2.23 (21-53)
Duration of diabetes (yr)	18.5 ± 1.52 (8-33)	16.6 ± 1.88 (7-39)
Body mass index (kg/m^2)	24.0 ± 0.66 (20.2-32.5)	22.7 ± 0.57 (18.6 ± 27.4)
Insulin dosage (IU/d)	39.6 ± 3.08 (20-71)	42.4 ± 2.72 (22-74)
Mean daily blood glucose (mg/dl)	179.4 ± 10.66 (121-304)	181.0 ± 9.08 (131-263)
Fasting blood glucose (mg/dl)	189.0 ± 14.05 (99-306)	171.6 ± 11.32 (94-275.7)
Systolic blood pressure (mmHg)	132.4 ± 2.60 (105-160)	135.5 ± 3.13 (120-160)
Diastolic blood pressure (mmHg)	82.6 ± 1.59 (65-95)	83.7 ± 1.37 (70-90)
HbA_{1c} (%)	8.0 ± 0.53 (3.9-13.5)	7.8 ± 0.33 (5.2-10.4)
Total serum cholesterol (mg/dl)	181.8 ± 5.33 (128-225)	189.8 ± 6.75 (143-240)
HDL cholesterol (mg/d)	56.3 ± 3.23 (33-83)	47.2 ± 2.17 (28-62)
Triglycerides (mg/dl)	92.5 ± 10.83 (50-247)	120.5 ± 10.34 (47-205)

Of the 17 pairs who completed the study 1 reached the endpoint at the 6th mo and 3 at the 12th mo because of the development of proliferative retinopathy (in both subjects in the pair of the 6th mo and in 1 of the pairs of the 12th mo, and in only one subject in the other two pairs).

Glycaemic control during CSII-CIT treatments

Mean blood glucose (MBG) was similar in the two groups at the beginning of the study, but a significant difference was evident from the 6th mo, characterized by a rapid reduction of MBG in CSII treated patients, which was maintained throughout the study (Fig. 2). As an effect of the increased number of control visits a tendency to a reduction of MBG was observed also in the CIT treated group which reversed from the 12th mo onward to return to the initial values at the end of the study.

A reduction of the HbA_{1c} levels was observed in the CSII group from the beginning of the study until the 12th mo, and remained stable thereafter. In the CIT treated group no significant modifications of the HbA_{1c} levels occurred in the first year of observation, while a tendency to deterioration was evident at the 12th and 24th mo. A significant differ-

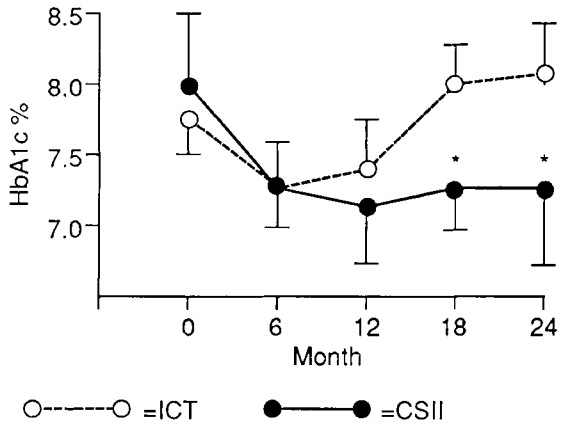

Fig. 3 - *Glycosylated haemoglobin (HbA_{1c}) of both treatment groups during the study. At baseline CSII and CIT are statistically comparable. Conversely, at the 18th and at 24th mo HbA_{1c} appears to be significantly lower in CSII than in CIT. *= $p < 0.05$.*

Table 2 - *Pairs classified according to the final retinal status of their components.*

		CIT			
		I	S	W	Total
CSII	I	0	1	1	2
	S	0	3	5	8
	W	0	4	5	9
Total		0	8	11	19

I = Improved; S = Stable; W = Worsened.

ence was therefore evident between the two groups in the final period of the study (Fig. 3).

Qualitative evaluation of retinal changes

The degree of agreement between the 3 groups of ophthalmologists, measured by means of K-reliability index, was K = 0.52 (SE 0.086, $p < 0.001$). At the baseline, in each pair the retinal status was similar between the two components, as also shown by the quantitative evaluation (see below). Table 2 shows retinal status at the end of the study of the 19 couples of patients. Twenty subjects (9 CSII and 11 CIT showed deterioration of the ischaemic areas; out of those, 7 (4 CSII and 3 CIT) progressed to proliferative changes which required prompt photocoagulation; in 16 patients (8 CSII and 8 CIT) no significant modification was observed. In 2 patients (both CSII) a reduction of ischaemic areas was documented. The McNemar test applied to the data shown in Table 2, aggregating rows and columns considering "not worsened" both improved and stable patients and "worsened" the remaining, did not show any significant association between evolution of ischaemia and insulin administration mode ($x^2 = 0.10$, $p < 0.10$). However, it is to be pointed out that a slightly better outcome in retinopathy progression was found in the CSII rather than in the CIT group. Namely, 2 subjects improved, 8 were stable and 9 worsened with CSII treatment, whereas no patient improved, 8 were stable and 11 worsened with CIT. A comparison between patients with retinal worsening and those without retinal worsening, regardless of the pairs distribution, showed that no dif-

Table 3 - *Statistically different of metabolic parameters in patients with not worsened or worsened diabetic retinopathy.*

Time	Variables	Not worsened X ± SE	Worsened X ± SE	p* <
Baseline	—			
6th mo	MBG mg/dl	148.8 ± 4.50	168.6 ± 7.65	0.04
	SBP mm Hg	125.1 ± 3.78	136.2 ± 3.03	0.03
	DBP mm Hg	79.9 ± 1.86	86.0 ± 2.19	0.05
	TG mg/dl	84.2 ± 7.94	118.2 ± 13.25	0.04
12th mo	SBP mm Hg	126.7 ± 3.10	136.7 ± 3.73	0.05
18th mo	HbA_{1c} %	7.1 ± 0.32	8.3 ± 0.33	0.02
24th mo	—			

(*) Significance level from Student's *t* test.
MBG = Mean daily blood glucose; SBP and DBP = systolic and diastolic blood pressure, respectively; TG = triglycerides; HbA_{1c} = glycosilated haemoglobin.

ference was evident at the baseline in the metabolic parameters (Table 3). At the 6th mo the two groups differed for mean daily BG, systolic and diastolic blood pressure and triglycerides (higher in the worsened group); at the 12th mo the two groups differed only for systolic blood pressure; and at the 18th mo only for HbA_{1c}. At the 24th mo they did not differ as to any of the parameters. It is worth noting that all the patients maintained normal visual acuity at the end of the study. No significant change as far as anterior segment was evident at the endpoint. In no case did rubeosis iridis develop. Intraocular pressure remained normal in all the patients.

Quantitative evaluation

A pilot study was carried out to evaluate the Dokumator method. Fluoroangiographies relevant to fields 1 and 2 were read by two ophthalmologists on a sample of 8 subjects with background diabetic retinopathy. Two angiographies were performed on each subject within 3-4 days. The sample size of 8 subjects was necessary to provide a power greater than 0.8 to detect a mean difference of at least 700 Dokumator Units between readers, once the variability of the phenomenon under observation has been stated in 500 Units. The method showed a high level of intra-rater and inter-rater consistency. A good correlation between the two readings of each ophthalmologist was found ($r' = 0.99$) as well as a correlation between the readings of the two ophthalmologists at each time ($r' = 0.99$). Good linear correlation was also found between the absolute differences (second reading minus first reading) of the readings of each ophthalmologists ($r = 0.96$, $p < 0.01$) and between the relative changes (second reading minus first reading out of the first reading) of the readings of each ophthalmologist ($r = 0.77$, $p < 0.05$). Once stated that within 3-4 days the retinal status of a subject cannot significantly change from a pathological point of view, and once the good reliability of the Dokumator method was recognized, the 99.9% confidence interval of Dokumator reading relative changes has been accepted as the interval within which a change must be considered different from zero by chance. For each subject, mean and variance of relative changes read by the two ophthalmologists were computed. A 99.9% confidence interval was then computed using as phenomenon variance the mean of the variances within each subject weighted with the respective degree of freedom. The resulting interval was that of extremes (—10.95, 12.83). According to this, a relative change was considered as "improvement" if < -10.95, "worsening" if > 12.83, "no change" if within the interval.

Because very good quality of the angiograms was required, Dokumator quantification of ischaemic areas in the two-year study was possible in 25 out of 38 patients of the present study. They included 10 pairs whose angiograms were available at the baseline and at the endpoint. At the baseline the mean of the differences in each pair (CSII minus CIT) was —6134 arbitrary Units. The Wilcoxon signed rank test showed that each pair entered the

Table 4 - *Multiple linear regression model association between changes of the ischaemic areas, metabolic parameters and blood pressure. (R-sq = 0.86; F = 6.39; p = 0.05).*

Variable	Regress. coeff.	S.E.	p-value	Stand. coeff.	R-sq contrib.
Intercept	—6660.8	1031.42	0.003	—1.98	
MBG	—170.2	48.33	0.024	—1.30	0.42
SBP	—216.9	52.82	0.015	—0.83	0.57

Variables in the model: The absolute change of retinal status over the 24 months of study is measured by the difference (24 mo-Baseline) of the Dokumator readings in the matched pairs: in other words the dependent variable of the model is expressed as $[(CSII\text{-}ICT)_{24}\text{-}(CSII\text{-}ICT)]$. As independent variables the average of the five evaluations of mean daily blood glucose, systolic and diastolic blood pressure, HbA_{1c} and body mass index were used.

Results of stepwise-linear-regression analysis. The statistics of the fitted model are shown within round brackets. R-sq = R-squared multiple correlation coefficient. F = F ratio to test the significance of the regression model, p = significance level.

For each statistically significant parameter are specified: Regress. coeff. = the regression coefficient (the negative coefficients shows a direct association between the parameters and the ischaemic deterioration stated the way in which the dependent variable has been expressed. S.E. = standard error of the coefficient, p-value = the statistical level of significance for that coefficient. Stand. coeff. = the value of the standardized coefficient (for direct comparisons between coefficient of independent variables expressed with different measure unit). R-sq contrib. = the contribution to R-squared that is the amount by which R-squared would be reduced if that variable were removed from the regression equation.

study with a sufficient comparable degree of ischaemia ($W = 9$, $p = 0.067$). Nevertheless, to verify the hypothesis that the different treatment influences the retinal evolution, changes with respect to the baseline were considered. At the endpoint the absolute change (final minus basal value) as well as the relative change (absolute change out of the basal value) was significant ($W = 1$, $p < 0.015$, Wilcoxon signed rank test for the former; mean $= 0.67$, SE $= 0.30$, N $= 9$, t $= 2.24$, $p < 0.05$, paired Student's t test for the latter).

Stepwise multiple linear regression analysis

This analysis showed that retinal deterioration, measured in 10 matched pairs and quantitatively measured by the Dokumator system, was significantly associated to systolic blood pressure, whatever measure of retinal evolution was considered. Table 4 shows the results of the best model estimation.

DISCUSSION

The aim of the present study was to investigate the effect of strict metabolic control achieved by CSII in Type I insulin-dependent diabetic patients on the progression of retinal ischaemia in diabetic retinopathy. In past years several studies have already tried to assess the benefits of intensified insulin treatment on background diabetic retinopathy (6, 9). However, it is to be pointed out that the large majority of previous investigations have taken into consideration diabetic patients showing a wide spectrum of retinal abnormalities ranging from mild background retinopathy only with few microaneurisms to advanced preproliferative or even proliferative retinopathy. Moreover, it has been postulated that diabetic retinopathy could be paradoxically deteriorated by a strict metabolic control (7, 8) consequent to a rapid near-normalization of BG levels.

The rationale of the present study was the recruitment of a diabetic population strictly characterized by a well defined retinal abnormality, that is areas of capillary non-perfusion, in order to verify the effects of CSII in comparison with CIT, precisely at this stage of retinal deterioration. A second feature of the present study was an analytical approach to retinal evaluation, using not only a qualitative assessment of retinal morphology, but also a quantitative measurement of the capillary-free areas by Dokumator Zeiss technique (11). To our knowledge, this is the first report on the effects of intensified insulin treatment on retinal microangiopathy, based also on a quantitative assessment of retinal ischaemic changes.

Our findings confirm previous observations that CSII achieves a better metabolic control than CIT. Furthermore, a better glycaemic control was neither associated with any rapid deterioration of retinal morphology, nor after one (21) or two years treatment was a significant worsening observed. On the contrary, the increase in the dimensions of the ischaemic areas was lower in the CSII than in the CIT group after two years treatment, suggesting that a good metabolic control could reduce the progression of diabetic retinopathy. Eventually, a further interesting finding of the present study is that higher blood pressure, although, within the range of normal values (140 mmHg systolic and 90 mmHg diastolic pressure), is associated with the progression of the diabetic retinopathy, irrespective of the degree of metabolic control. It is to be pointed out that the difference in the metabolic control between the two insulin regimens (CSII and CIT), was not so clearly marked as in other reports. Namely, DCCT data (22) indicated that the two treatment regimens did result in a more substantial difference in metabolic control than that found in the present study. At the 12th mo HbA_1 level was 8.56% in diabetics on conventional therapy and 6.70% in the patients on intensified insulin therapy, whereas HbA_{1c} value at the correspondent time was 7.1% in our CSII patients and 7.4% in those on conventional therapy. On the other hand, it is to be pointed out that we have also considered in the CIT group those patients with three insulin administrations per day, whereas the DCCT study included in the conventional therapy regimen only subjects with two daily injections. From a general point of view, all the subjects participating in our protocol study were educated to achieve a good metabolic control. Thus, both CSII and CIT patients showed an improved metabolic control at the 12th mo in comparison with baseline values. However at the second year, patients on CIT therapy were back to baseline values, whereas patients on CSII maintained HbA_{1c} levels which were significantly lower than those exhibited before entering the study protocol.

With regard to the retinal outcome, quantitative

evaluation using Dokumator Zeiss approach showed that the improved metabolic control found with the CSII treatment was associated with a retarded progression of ischaemic retinopathy in comparison with ICT regimen. Conversely, qualitative evaluation, though taking into account a wider retinal field, failed to demonstrate a significant difference of the retinal outcome between CSII and CIT. Some considerations should be made in regard to this apparent discrepancy. First, even though the two treatment regimens did not reach a statistical difference at the endpoint as far as qualitative assessment of the ischaemic changes is concerned, a tendency to a slower progression of retinopathy in patients treated with CSII seems evident. Secondly, all previous studies (22, 23), where evaluation of diabetic retinopathy was transformed in terms of improvement, no change or deterioration failed to demonstrate a better outcome of intensified insulin therapy when compared to conventional treatment. Only when results of the Steno Study (23) and those of the Oslo Study (24) were cumulated together, the better metabolic control found in CSII was associated with a significantly better outcome of retinopathy.

The present results considered as a whole seem to support the view that, even though in our patients CSII does not prevent the development of proliferative retinopathy, the deterioration of retinal microangiopathy could be retarded by strict metabolic control achieved by CSII, even at a relatively advanced stage such as ischaemic retinopathy. Finally, a significant correlation was found in the present study between the evolution of retinopathy and the levels of the arterial blood pressure, suggesting that the retinal deterioration is associated with the degree of blood hypertension as well. An interesting finding of the present study is that the majority of the diabetic patients exhibited blood pressure patterns within the range of normal values. Thus, it can be suggested that also a slight increase in blood pressure within the normal range could be associated with a deterioration of the retina. A similar finding has been reported in diabetic patients on insulin therapy with regard to evolution of nephropathy (25).

In conclusion, our results indicate that 1. an amelioration of metabolic control is associated with a slightly better evolution of diabetic retinopathy; 2. an important related parameter in the evolution of ischaemic toward proliferative retinopathy seems to be the systolic blood pressure. On the other hand, it can be suggested that at an equal degree of systolic blood pressure, a strict metabolic control could play a favourable role.

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