Continuous Subcutaneous Insulin Infusion (Mill-Hill Infuser) Versus Multiple Injections (Medi-Jector) in the Treatment of Insulin-dependent Diabetes Mellitus and the Effect of Metabolic Control on Microangiopathy

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The present study was designed to compare continuous subcutaneous insulin infusion (CSII) using the Mill-Hill Infuser (Muirhead Medical Products Ltd., London, England) with multiple injections (MI) using the Medi-Jector (Derata Corporation, Minneapolis, Minnesota) in the treatment of insulin-dependent diabetes mellitus (IDDM), and to assess the effect of glucose control on diabetes complications. Twelve diabetic subjects were treated 3 mo with CSII and 3 mo with MI (bedtime ultralente and premeal boluses of regular insulin) in a randomized fashion. Prestudy preprandial/postprandial glucose levels were 147–215 mg/dl and improved to 108–138 mg/dl during CSII, and to 115–139 mg/dl during MI with glycosylated hemoglobin of 12.9%, 9.1%, and 8.7%, respectively. This improved glucose control with either CSII or MI was associated with an increase in sural nerve conductivity from 42.9 to 45 m/s and a decrease in proteinuria from 1.9 to 0.5 g/24 h. The 24-h insulin dose consisted of 45 U before the study, 44 U during CSII, and 56 U during MI. After the study, seven patients opted to continue with the Mill-Hill Infuser, and five with the Medi-Jector. We conclude the following: (1) treatment with both the Mill-Hill Infuser and the Medi-Jector was well accepted by the patients and resulted in similar improvement in measured blood glucose and glycosylated hemoglobin; (2) this improved metabolic control was associated with an increased nerve conductivity and a decreased protein excretion; and (3) MI required 20% more insulin than CSII to achieve similar glycemic control. DIABETES CARE 1984; 7:331–37.

Substantial evidence seems to implicate hyperglycemia in the pathogenesis of diabetic microangiopathy.[1] In a retrospective study of more than 4000 diabetic patients over a 25-yr period Pirart[2] showed a positive correlation between the lack of control of diabetes and the appearance and progression of retinopathy, nephropathy, and neuropathy. Also supporting the hyperglycemia hypothesis is the observation that patients undergoing pancreatectomy for different reasons eventually develop the same degenerative lesions.[3] The kidney from a normal donor transplanted into a diabetic subject also develops diabetic nephropathy.[4] Experimental diabetes in animals is also associated with similar complications.[5]

These observations have led to major efforts in the development of new approaches in the treatment of insulin-dependent diabetes mellitus (IDDM) in the hope of achieving better glycemic control. This was facilitated by the development of new techniques to measure capillary blood glucose, making home blood glucose monitoring feasible.[6–11] Another new technique of major importance was the determination of glycosylated hemoglobin, which correlates with the degree of glucose control.[12–14] It therefore became possible to approach the treatment of diabetes mellitus in a more physiologic way, and new insulin regimens delivered by either multiple injections (MI) or mechanical infusion pumps have been proposed.[15–25]

These new types of treatment of diabetes mellitus are more physiologic in design, and have made it possible to achieve long-term normoglycemia.[17–19] Such normoglycemia has been shown to prevent the complications associated with pregnancy in diabetic mothers.[26] Some studies have suggested that good glucose control can result in regression of microangiopathy associated with diabetes.[27–29] Others, however, have suggested that long-term improvement of metabolic control does not reverse diabetic microangiopathies.[30]

We have recently reported the long-term effectiveness of

continuous subcutaneous insulin infusion (CSII) using the Mill-Hill Infuser (Muirhead Medical Products Ltd., London, England) using algorithms related to the carbohydrate content of the patients' meals.[19] We have also shown that such good control had a beneficial effect on platelet function and neuropathy.

Because of the high cost of pump therapy, and certain inconveniences reported by some of the patients, we wished to explore the use of the same algorithms with MI. To increase acceptability by the patients, MI was administered by means of an automatic jet injector (Medi-Jector, Derata Corporation, Minneapolis, Minnesota). We have compared the efficiency of CSII (Mill-Hill Infuser) with that of MI (Medi-Jector) in achieving metabolic control in IDDM, and have assessed the effect of such metabolic control on neuropathy and nephropathy.

METHODS

Subjects. Twelve insulin-dependent diabetic subjects (mean age, 27 yr; mean duration of disease, 15 yr) took part in the study. All were within 20% of ideal body weight; all had signs of retinopathy, three having signs of neovascular proliferation; and all had decreased sural nerve conduction, two having no measurable conduction. Eight of the 12 subjects had significant proteinuria (Table 1).

Protocol. The protocol was approved by the Ethic Committee, and all subjects signed informed consent. All subjects were treated by CSII using the Mill-Hill Infuser for 3 mo, and by MI using the Medi-Jector, also for 3 mo; half of the subjects started with the pump and half with the Medi-Jector. All patients were admitted to the Clinical Research Unit at Hotel-Dieu de Montreal Hospital to initiate either treatment. During their hospitalization they learned how to operate the pump or the Medi-Jector, how to calculate the amount of carbohydrate in their diet, and how to modify their insulin doses according to specific algorithms. Some of the subjects were maintained on the pump or on MI for more than 3 mo when the Clinical Research Unit was closed during the summer months. Nevertheless, the parameters were measured after 3 mo of treatment with either the Mill-Hill Infuser or the Medi-Jector. The mean total time of treatment with the pump and the Medi-Jector for the whole group was 8 ± 0.3 mo. A diabetic diary recording the insulin dose, the preprandial (a.c.), and postprandial (p.c.) blood sugar measured at home, and the meal content was obtained before the study and at the end of each 3-mo treatment period during three representative days (two during the week and one during the weekend, but never on two consecutive days) and used for data analysis. Glycosylated hemoglobin, glycosuria, proteinuria, and nerve conduction were also measured before the study and at the end of each 3-mo treatment period.

Algorithm. On the basis of our previous results,[19] the initial basal rate was set at 50% of the previous insulin dose and was given as a continuous infusion of regular insulin (Eli Lilly and Company, Indianapolis, Indiana) in the patients on the pump and as ultralente (Eli Lilly and Company) at 22 h in the patients on the Medi-Jector. The boluses were given 20 min before meals as regular insulin in both treatments according to the following initial schedules: 2.7 U/20 g carbohydrate before breakfast and 1.8 U/20 g carbohydrate before other meals and snacks containing more than 20 g of carbohydrate. The target glucose level was 70–120 mg/dl before meals and <150 mg/dl after meals (1 h). All blood glucoses <50 mg/dl and >180 mg/dl were considered undesirable. All subjects performed home blood glucose monitoring at least three times a day: always on rising in the morning and at least two more determinations at a.c., p.c.,

TABLE 1
Clinical data

Patient no.	Age (yr)	Sex	Duration of diabetes (yr)	Complications		
				Retinopathy*	Nephropathy†	Neuropathy‡
1	18	M	7	+	−	+
2	26	F	15	+	+	+
3	19	F	17	+	+	+
4	40	M	20	+	−	+
5	25	F	8	+	−	+
6	27	F	22	+	+	+
7	19	M	5	+	+	+
8	33	F	23	+	+	+
9	28	M	23	+	+	+
10	28	M	4	+	−	+
11	27	F	19	+	+	+
12	32	F	20	+	−	+

*Retinopathy, presence of microaneurysms.
†Nephropathy, presence of >0.2 g urinary protein per 24 h.
‡Neuropathy, decrease in sural nerve conductivity of more than 2 SD.

or bedtime in an alternating fashion to get at least two full profiles per week. Compliance was checked by going over the patient's notebook at each visit. Patients were instructed to readjust their insulin doses if their capillary glucoses deviated from the recommended target for two consecutive days. The basal rate was increased or decreased by 1 U/24 h if the fasting blood glucose was >120 mg/dl or <70 mg/dl. The boluses were increased or decreased by 0.2 U/20 g of carbohydrate if the 1-h p.c. blood glucose was >150 mg/dl or below the a.c. blood glucose. The 1-h p.c. glucose was chosen mainly as a matter of convenience; particularly for those working, and on the basis of previous experience.[19] Patients were also instructed to add 2 U of regular insulin to their boluses for every 100 mg/dl above recommended glucose goal.

Analysis. Home blood glucose monitoring was performed by the patient, using a Dextrometer or a Glucometer and Dextrostix (Miles Laboratory, Elkhart, Indiana).[11] The accuracy of the patient's determination was checked during hospitalization (coefficient of variation = 8.2 ± 2%). Glycosylated hemoglobin in venous blood was measured by column chromatography (Bio-Rad procedure kit, Richmond, California). Nerve conduction velocity was measured by EMG; glycosuria, by standard laboratory method; and proteinuria, by the quantitative sulfosalicylic acid method.[31] The M-value, an index of variation from the norm, was calculated according to Schlichtkrull[32] as modified by Service.[33] Statistical comparisons were made by means of paired *t* test.

RESULTS

Effect of CSII (Mill-Hill Infuser) and MI (Medi-Jector) on metabolic control. The preprandial (a.c.) and postprandial (p.c.) capillary blood glucoses measured during the three representative days for each meal during conventional therapy, CSII, and MI are illustrated in Figure 1. Each value represents the mean ± SEM of 36 determinations. While both CSII and MI were significantly improved compared with conventional therapy, there was no demonstrable difference between the two modes of intensive insulin therapy. The a.c./p.c. glucose was 147 ± 9/215 ± 10 mg/dl with conventional therapy, 108 ± 6/138 ± 7 mg/dl with CSII and 115 ± 8/139 ± 6 mg/dl with MI. During those three representative days, the incidence of undesirable high blood glucose was 42% with conventional therapy and decreased to 11% and 13% during CSII and MI, respectively. The incidence of undesirable low blood sugar was 1.2% before intensive therapy and increased slightly but significantly to 1.9% and 3.8% with the pump and the Medi-Jector. However, none of these low blood sugars during intensive therapy was symptomatic or required treatment, only one being below 40 mg/dl (35 mg/dl). In fact, patients who had been symptomatic during conventional therapy, even with blood glucose in the normal range (70–100 mg/dl), were no longer symptomatic during intensive insulin therapy. The M-value was calculated from the glucose determinations of the three representative days. Each value is calculated from 216 determinations and as such

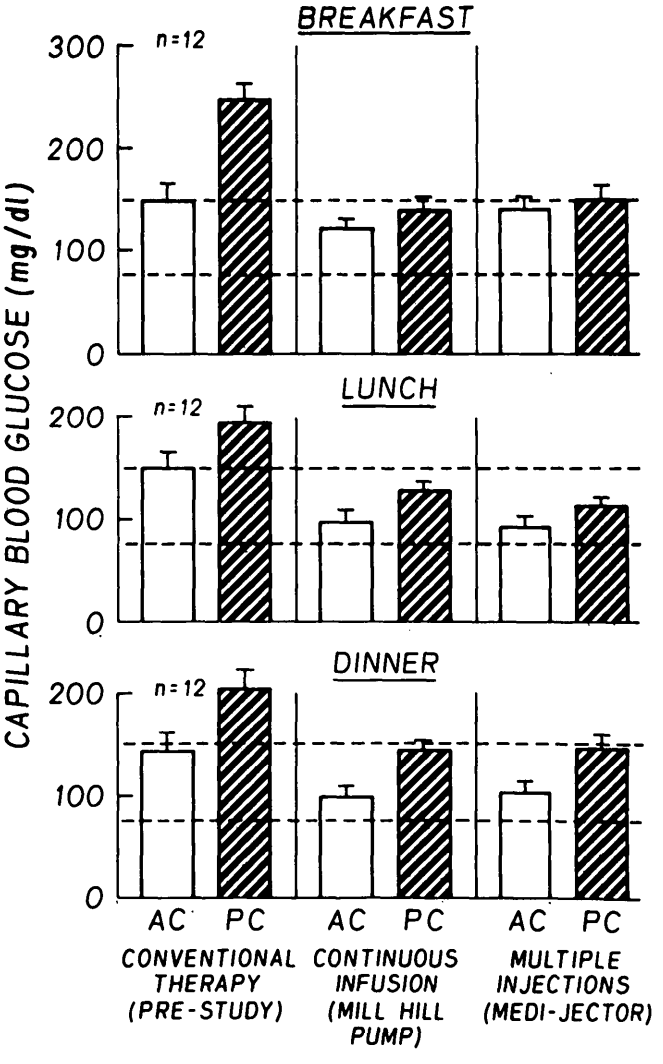

FIG. 1. Effects of conventional therapy, CSII, and MI on preprandial (open bars) and 1-h postprandial (hatched bars) capillary blood glucose for morning, midday, and evening meals. Each bar represents the mean ± SEM of 36 determinations from 12 subjects.

represents within-day and day-to-day glucose variability. The M-value was 47.7 ± 5.7 during conventional therapy, 10.4 ± 2.8 during pump treatment, and 10.9 ± 3.2 during Medi-Jector treatment (Table 2). Glycosuria before the study was 30.7 ± 17 g/24 h, and decreased to 5 g/24 h with CSII and MI (Table 2). Glycosylated hemoglobin was 11.9 ± 0.6% during conventional therapy and decreased significantly to 9.1 ± 0.3% and 8.7 ± 0.4% with the pump and Medi-Jector, respectively (Table 2); the difference between the pump and the Medi-Jector was not significant. Thus, the Mill-Hill pump and the Medi-Jector were equally effective in controlling the a.c. and p.c. blood glucose.

Effect of metabolic control on nerve conductivity and proteinuria. Since the conduction velocity of all nerves measured by EMG varied in the same direction, we are presenting only the data from the sural nerves as a matter of simplicity. Two

TABLE 2
The effects of three insulin regimens on capillary blood glucose variations (M-values), glycosuria, and glycosylated hemoglobin*

	Conventional therapy	Continuous infusion (Mill-Hill Pump)	Multiple injections (Medi-Jector)
Capillary blood glucose (M-values)	47.7 ± 5.7	10.4 ± 2.8	10.9 ± 3.2
Glycosuria (g/24 h)	30.7 ± 16.6	4.2 ± 1.6	5.7 ± 2.4
Glycosylated hemoglobin (%)	11.9 ± 0.6	9.1 ± 0.3	8.7 ± 0.4

*Data are expressed as mean ± SEM (N = 12).

of the subjects had no measurable potentials at either sural nerve during conventional therapy. Interestingly, in those two subjects, improved glucose control was associated with the reappearance of potentials at the end of the study. For statistical purposes the zero values were not computed; thus, the initial conduction velocity value was in reality lower than indicated in Figure 2. Figure 2 shows that the sural nerve conductivity, which was 42.8 ± 1.2 m/s during conventional therapy, was not affected after 3 mo of improved control (42.8 ± 1.4 m/s), but increased significantly (45.0 ± 1.0 m/s, $P < 0.05$) by the end of the study. This is still, however, below the norm (49 ± 2 m/s).[19]

Eight of the 12 subjects were found to have significant proteinuria before the study (1.9 ± 1.1 g/24 h; range = 0.21–9.8 g/24 h). Figure 3 illustrates the proteinuria per 24 h corrected for creatinine excretion. During conventional therapy the mean proteinuria per gram of creatinine/24 h was 1.9 ± 1.0, decreased to 0.98 ± 0.43 after 3 mo of better glucose control and improved further to 0.43 ± 0.24 by the end of the study.

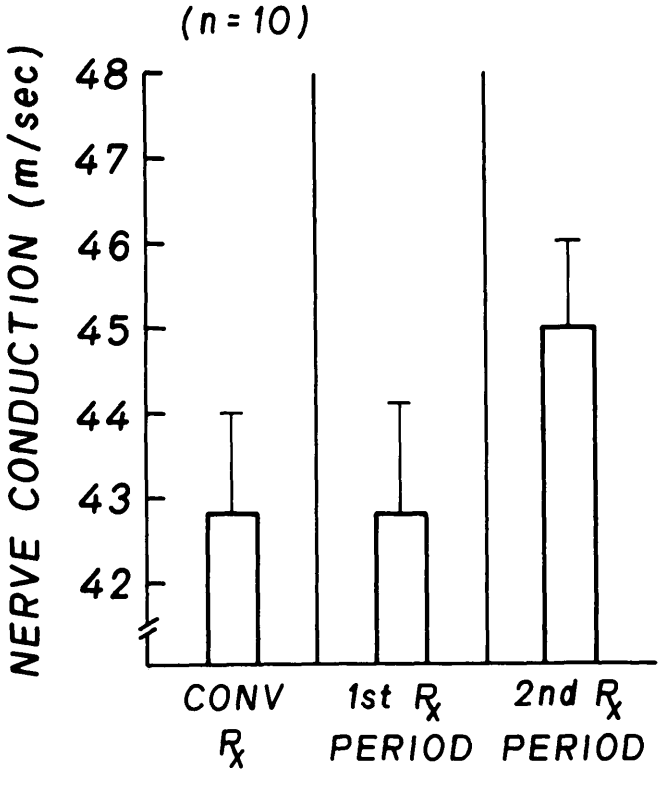

FIG. 2. Sural nerve conductivity during conventional therapy (Conv. Rx), and after the first (1st Rx) and second (2nd Rx) 3-mo periods of intensive insulin therapy by either CSII or MI. Mean ± SEM (N = 10).

The final outcome in nerve conductivity and proteinuria was not affected by whether the initial intervention was with the Mill-Hill Infuser or the Medi-Jector.

Insulin dose required during CSII (Mill-Hill Infuser) and MI (Medi-Jector) to achieve good metabolic control. There was no difference between insulin requirement during continuous infusion (43.9 ± 2.9 U/24 h) and that during conventional therapy (44.7 ± 4.2 U/24 h), despite better metabolic control with the former. However, with MI a significantly higher dose of insulin was required (56.1 ± 5.9 U/24 h, $P < 0.01$) to achieve similar glucose control. If the bolus and basal doses are analyzed separately, it appears that the basal doses are significantly different (18.7 ± 1.9 U/24 h with the Mill-Hill pump versus 27.2 ± 2.4 U/24 h with the Medi-Jector, $P < 0.02$) while the bolus doses are not (Figure 4).

Patients' choice of therapy. At the end of the study seven of the patients chose to continue with the Mill-Hill pump and five with the Medi-Jector. None chose to revert to conventional therapy with syringe and needle.

DISCUSSION

The present study demonstrates that both CSII by means of the Mill-Hill Infuser and MI injections with the Medi-Jector resulted in similar control of measured blood glucose and glycosylated hemoglobin. This confirms the observations made by other groups.[17,18,24,25]

To achieve such tight control of the blood glucose, the insulin dose had to be adjusted frequently for the first week or two, but after that, minor adjustments could be made weekly. This resulted in a marked decrease in the incidence of undesirable high blood glucose. Though there was a slight increase in the incidence of low blood sugar, there was a decrease in the incidence of symptomatic hypoglycemia. This suggests that lower blood glucoses were better tolerated during

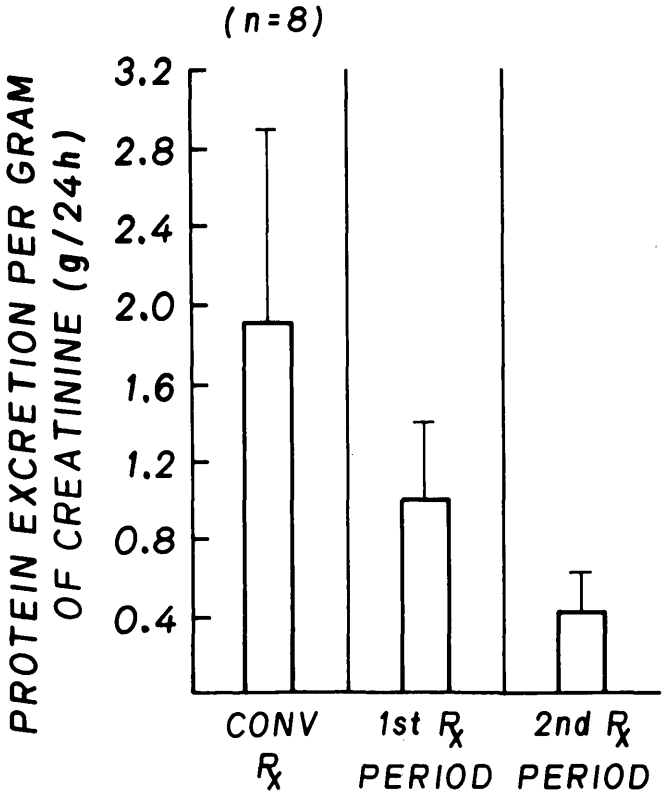

FIG. 3. Proteinuria after correction for creatinine excretion during conventional therapy (Conv. Rx), and after the first (1st Rx) and second (2nd Rx) 3-mo periods of intensive insulin therapy by either CSII or MI. Mean ± SEM (N = 8).

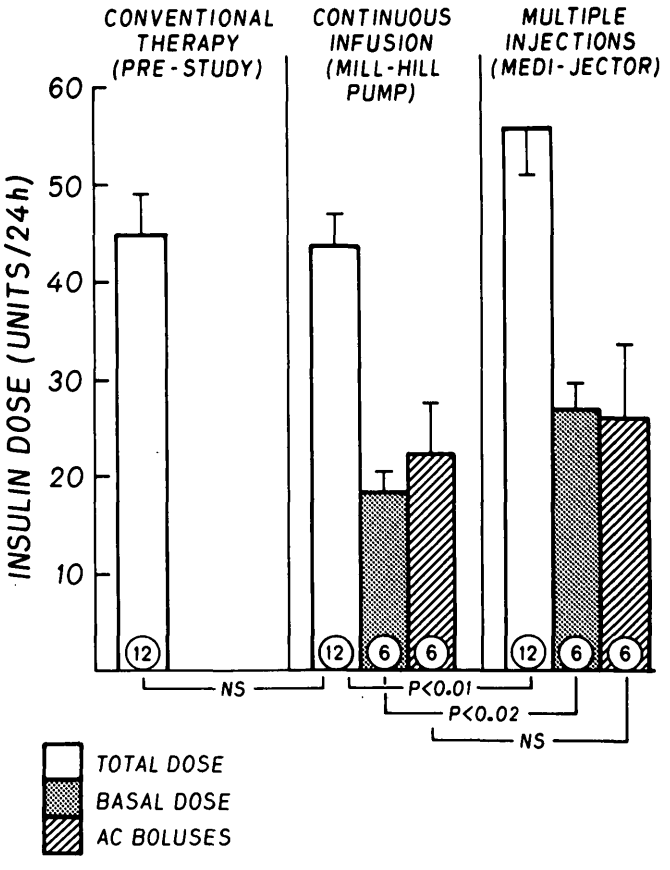

FIG. 4. Insulin requirements during three treatment regimens. Mean ± SEM (N = 12).

intensive insulin therapy, most likely due to better distribution of the insulin and consequently smaller excursion of blood glucose.

It also indicates that the Medi-Jector is a good alternative to conventional syringe and needles, as well as to the insulin pump, as a means of insulin administration. Not only did it achieve good glucose control but it was well accepted by the patients, as indicated by the fact that nearly half the patients opted for the Medi-Jector. The reasons for their choice were: (1) Some preferred the Medi-Jector because they were not tied to it and thus had a certain sense of freedom; this was particularly important for those regularly involved in swimming. (2) Others preferred jet injections because of the psychological impact of needles. Another advantage of the Medi-Jector to the syringe and needle is the subcutaneous distribution of insulin administered by jet injection. The insulin spreads evenly in the subcutaneous tissue and for that reason it is suggested that the hormone is better absorbed to give earlier peak levels and higher free insulin levels.[34,35] It has also been shown that jet injection is less likely than conventional needle injection to cause lipodystrophy.[36] For these reasons we believe that jet injection using the Medi-Jector is a recommendable alternative.

On the other hand, to achieve similar metabolic control, 20% more insulin was required with MI. The question therefore arises as to whether MI results in higher insulinemia. Since it has been suggested that hyperinsulinemia could play a role in diabetic complications,[37,38] particularly macroangiopathy, this could be of major concern. However, if we analyze separately the basal dose that was given as ultralente at bedtime from the a.c. boluses, it becomes evident that the boluses are similar to those of the pump, and that only the basal dose given as a single injection of ultralente is higher than the basal dose of the pump. This could be interpreted as meaning that ultralente is less efficient than regular insulin or is degraded further at the site of injection. Another possibility is that with MI, higher insulin levels are required to achieve similar glucose control. This needs to be further investigated.

The effects of good glucose control for 8 mo on the microangiopathies were very encouraging. While no significant change in the sural conduction was observed after the first 3-mo treatment period, a definite improvement was demonstrated in all but two of the 12 subjects studied by the end of the second 3 mo of intensive insulin therapy. This confirms our previous study[19] and those of Tamborlane et al.[28] and Ward et al.[39] showing increased nerve conduction velocity with improved blood glucose control.

An early marker for the onset of renal dysfunction in

diabetes is the development of proteinuria, particularly albuminuria.[40] Viberti et al.[41] have suggested that proteinuria could be normalized if strict metabolic control could be maintained. Our data support Viberti's observation since mean proteinuria in our patients decreased from 1.9 ± 1.0 g to 0.98 ± 0.43 g after the first 3 mo of tight per-gram control, and improved further to 0.43 ± 0.24 g/g creatinine/24 h after 8 mo of good glucose control. This, however, contrasts with observations made by Tamborlane et al.,[30] who showed an early decrease in proteinuria that was not sustained when followed over a 12-mo period. These discrepancies are difficult to explain. It is possible that nephropathy could be reversed with good diabetes control early in its course but that beyond a certain point it would progress independently of the degree of glucose control. Other concomitant problems, such as hypertension, could also influence the progression of nephropathy. Nevertheless, the regression of the glomerular lesions seen in diabetic rats treated by pancreatic islet transplantation[42] is in line with our observations.

Our results therefore indicate that both CSII and MI are equally effective in normalizing the measured blood glucose and glycosylated hemoglobin, and show that the Medi-Jector is a recommendable alternative method for insulin administration. This study also shows that the basal dose must be higher when MI is used. Finally we have found a net improvement in sural nerve conduction velocity and in proteinuria after 8 mo of good metabolic control.

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