The Benefits of Metformin Therapy During Continuous Subcutaneous Insulin Infusion Treatment of Type 1 Diabetic Patients

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OBJECTIVE — This study was designed to assess the insulin-sparing effect of oral administration of metformin along with a continuous subcutaneous insulin infusion (CSII) for the treatment of type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 62 patients (25 women and 37 men) were studied in a monocenter, randomized, double-blind placebo-controlled study, comparing metformin (850 mg b.i.d.) with placebo in association with CSII during a 6-month period.

RESULTS — Treatment with metformin was associated with a reduction in daily insulin requirements between V0 and V6 of -4.3 ± 9.9 units ($-7.8 \pm 18\%$) compared with an increase with placebo treatment of 1.7 ± 8.3 units ($2.8 \pm 12.7\%$) ($P = 0.0043$). A decrease in basal requirement of insulin was also observed in patients treated with metformin of -2.6 ± 3.2 units ($-7.9 \pm 23.8\%$) compared with an increase with placebo treatment of 1.9 ± 5.7 units ($8.8 \pm 27.1\%$) ($P = 0.023$). HbA$_{1c}$ remained unchanged in treatment with metformin and placebo between V0 and V6. The number of hypoglycemic events (<60 mg/dl) was similar in both groups. Significant reductions of total cholesterol ($P = 0.04$) and LDL cholesterol ($P = 0.05$) were observed in patients treated with metformin. Gastrointestinal events, including diarrhea and abdominal pain, were reported in three patients in the metformin group who discontinued the trial. Mild or moderate gastrointestinal side effects were also reported in eight patients treated with metformin and two patients treated with placebo ($P = 0.069$).

CONCLUSIONS — Metformin was found to be a safe insulin-sparing agent, when used in combination with CSII for the treatment of type 1 diabetes.

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The Diabetes Control and Complications Trial (DCCT) (1) clearly demonstrated that intensive insulin therapy to achieve near normoglycemia reduces the risk of development and progression of long-term complications of type 1 diabetes but often leads to an increase in hypoglycemic episodes. Continuous subcutaneous insulin infusion (CSII) can reduce the rate of severe hypoglycemia in type 1 diabetes, as compared with that seen in patients receiving multiple daily injections (2), although the results remain controversial (1,3). It has also been demonstrated that pump therapy using insulin analogs improved blood glucose control without increasing the incidence of severe hypoglycemia (4,5).

Metformin is a biguanide that has been used in management of type 2 diabetes for more than 40 years. It improves glycemic control by enhancing insulin sensitivity in the liver (leading to a decrease in basal hepatic glucose production) and muscle (leading to an increase in glucose uptake) (6). In insulin-treated type 2 diabetic patients, the use of metformin improves insulin sensitivity and glycemic control, leading to a reduction in the daily insulin requirement (IR) (7–9). In type 1 diabetes, addition of metformin to insulin therapy has been assessed in a few trials involving few patients or in uncontrolled studies of short duration (10–12). These studies suggested a mean reduction in IR of ~25% with a variation of 20–40%. In our study, involving the use of metformin in type 1 diabetic patients treated with CSII, the effect on blood glucose control, IR, and hypoglycemic episodes is reported.

RESEARCH DESIGN AND METHODS

Patient selection
The study was performed in a group of 62 type 1 diabetic patients. All were C-peptide negative (C-peptide <0.3 mmol/l

after intravenous injection of 1 mg glucagon). These patients had been selected from 225 diabetic patients treated with CSII at our outpatient clinic. All of the patients in the study had been treated by CSII for at least 1 year, had HbA_{1c} concentration <9%, had good compliance with home blood glucose monitoring, and had hypoglycemia awareness. Exclusion criteria were nonstable retinopathy, any disease (endocrine, infectious, or inflammatory) that significantly modifies blood glucose control, pregnancy, impaired renal function, and cardiac and hepatic dysfunction.

Study design

This study was a randomized, monocenter, double-blind, placebo-controlled parallel group trial (metformin versus placebo) of 6 months' duration. After a 2-month placebo run-in period, patients were randomized (V0) to receive either metformin (850 mg) or placebo twice daily and were instructed to take the treatment during or at the end of breakfast and dinner. After randomization at V0, patients were evaluated at 8-week intervals (V2, V4, V6), when clinical data, including adverse effects, were assessed and protocol compliance, monitored by pill counting, was recorded. The daily IRs during the preceding 7 days and body weight were also recorded. IRs were evaluated separately, according to basal rate and bolus doses (mean of the three premeal bolus) given. Biological parameters, including HbA_{1c}, fasting blood glucose, hypoglycemic episodes, and lipid parameters, were also assessed.

The protocol was approved by the Ethical Committee of the University of Nancy (France), and written consent was obtained from all the patients after clear explanation of the trial.

Patient instructions

All patients were treated with regular insulin (Velosuline HM 100 IU/ml; Novo Nordisk A/S, Bagsvaerd, Denmark) by CSII, using an external pump (Minimed infusor MMT 506, 507c, and 508; Mini-Med Technologies, Northridge, CA) and deconnectable catheters (Tender set; Disetronic Medical Systems AG, Burgdorf, Switzerland and Sofset QR; MiniMed Technologies). The catheter infusion site was changed every 3 days. The patients had been taught to perform capillary blood glucose estimations before meals,

2 h after meals, and at bed time using a One Touch Profile memory meter (Lifescan, Roissy, France). The memory meter data were downloaded onto a computer (In touch program; Lifescan). Adjustments of the insulin doses were made by the patient, based on the results of self-monitoring of blood glucose (SMBG) as previously described (13,14) and by the investigator at each visit if needed. Premeal, postmeal, and bedtime target ranges were 80–130, 130–160, and 100–130 mg/dl, respectively. Supplemental doses were calculated using each patient's insulin sensitivity factor and target blood glucose level (15). The patients were instructed to record in a notebook all episodes of hypoglycemia in which the blood glucose level was <60 mg/dl. Severe hypoglycemia, as defined by the DCCT criteria (16), was also recorded. Patients were instructed to treat hypoglycemia with 10 g of oral glucose and 20 g of carbohydrates, to recheck the blood glucose in 20 min to ensure an adequate response, and to adjust their insulin dose in response to an unexplained low blood glucose level.

Recording of SMBG measurements

The time of all capillary SMBG measurements (date and hour) was recorded in the glucose meters. For the whole group of 62 patients, a total of 44,666 SMBG levels were recorded during the 6 months of the study.

A glucose meter (One Touch Profile; Lifescan) was given to each patient at randomization (V0), when treatment with placebo or metformin was begun. Consequently, the recorded SMBG levels were compared for each period of follow-up (V0–V2, V2–V4, and V4–V6), but not for the period preceding randomization (run-in period).

We analyzed the different intervals of time for SMBG measurements, according to the frequency of SMBG performance: fasting period (5:00–7:00 A.M.), lunch preprandial period (11:00 A.M. to 12:00 P.M.), dinner preprandial period (6:00–7:00 P.M.), postprandial periods (9:00–10:00 A.M. and 2:00–3:00 P.M.), and bedtime period (9:00–10:00 P.M.) assimilated as a postprandial period.

Assay methods

Blood samples were collected at each visit after a 12-h overnight fast. Plasma glucose was measured by the glucose oxidase

method (Beckman Glucose Analyzer; Beckman, Fullerton, CA). HbA_{1c} was measured by high-performance liquid chromatography on Biorex resins (Bio-Rad, Richmond, CA; normal range 4.3–6%). Total cholesterol and triglycerides were measured by immunoenzymatic assay (Bio-Mérieux, Marcy l'étoile, France). HDL cholesterol was measured after precipitation by phosphotungstic acid/manganese (Boehringer, Mannheim, Germany). LDL cholesterol was calculated using the Friedewald formula (17).

Statistical analysis

Results are expressed as means $\pm$ SD and are shown as means $\pm$ SE in Fig. 1. The primary end point evaluated was the reduction of IR associated with decrease or stability of HbA_{1c}. Secondary end points were number and severity of hypoglycemic episodes, effect on plasma lipids and weight, and clinical tolerance. Statistical analyses were performed on an intention-to-treat basis, and for patients interrupting the trial, final measurements were imputed by their last observation carried out values. Difference between metformin and placebo groups was assessed by a ANCOVA with treatment as the fixed factor and IR at randomization (V0) as an adjustment covariate. The mean change between the value at each visit and randomization in each group was assessed using Student's t test. Incidence of hypoglycemic episodes between the two groups was evaluated by ANOVA, and the frequency of severe hypoglycemia was evaluated using χ^2 test. The clinical relevance of the main results was assessed by responder analysis: a patient was considered a responder when HbA_{1c} was stable or improved, with a reduction of $\geq$20% in IR since randomization and without any severe hypoglycemic episodes. The response rate was compared between the two treatments by logistic regression, adjusting for initial IR and body weight. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS software (Version 6.1; SAS Institute, Cary, NC) in the Windows NT operating system.

RESULTS — A total of 62 patients (25 women, 37 men; 31 treated with metformin and 31 treated with placebo) were included and were eligible for the intention-to-treat analysis. Three patients in the metformin treatment group inter-

Total insulin needs
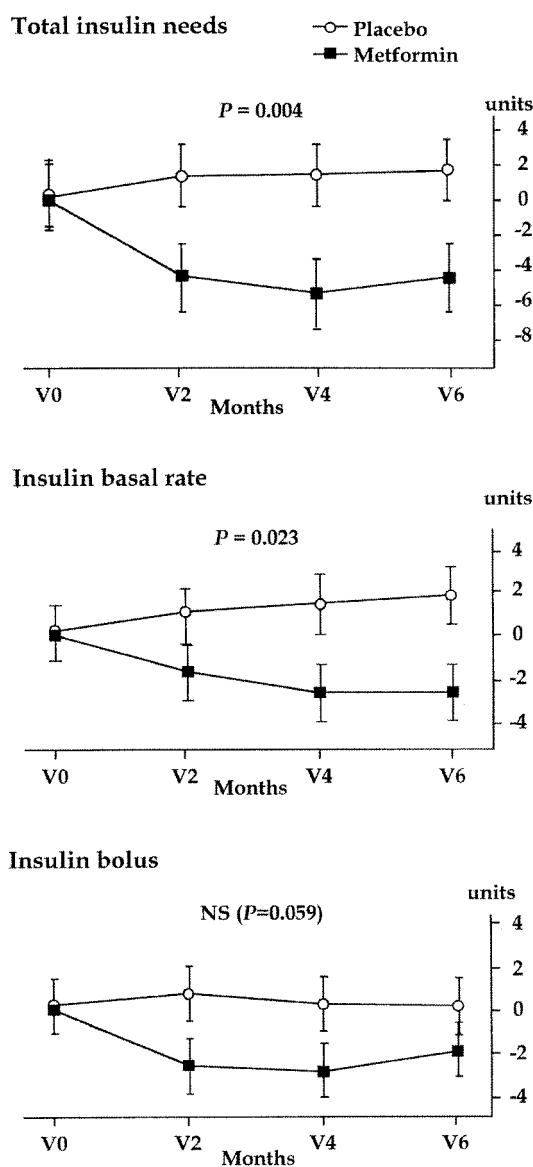
Figure 1—*Evolution of IR (total, basal, and bolus insulin needs) from V0 to V6 in type 1 diabetic patients during placebo (○) or metformin (■) treatment. Results are shown as means ± SE.*

rupted the trial because of drug intolerance. Compliance with treatment was 75% for patients who completed the study. Clinical and biological characteristics of the patients at randomization (V0) are shown in Table 1; no difference was noted between the two groups.

IR

A relative daily reduction in IR was observed in patients treated with metformin between V0 and V6 of -4.3 ± 9.9 units $(-7.8 \pm 18\%)$ compared with an increase in patients treated with placebo of 1.7 ± 8.3 units $(2.8 \pm 12.7\%)$ $(P = 0.0043)$ (Table 2, Fig. 1). The decrease in daily IR in the metformin group was significant between V2 and V6 (Table 2). At V6, the total daily insulin dose was lower in the metformin group than in the placebo group $(0.65 \pm 0.17$ vs. 0.74 ± 0.24 units $\cdot kg^{-1} \cdot day^{-1}$, $P = 0.086)$.

A decrease in basal requirements was observed in the metformin group between V0 and V6 of -2.6 ± 3.2 units $(-7.9 \pm 23.8\%)$ compared with an increase in the placebo group of 1.9 ± 5.7 units $(8.8 \pm 27.1\%)$ $(P = 0.023)$ (Table 2, Fig. 1). The decrease in basal requirements in the metformin group was significant from V4 to V6 (Table 2). Daily basal IR at V6 was lower in the metformin

group than in the placebo group $(0.27 \pm 0.10$ vs. 0.30 ± 0.11 units $\cdot kg^{-1} \cdot day^{-1})$.

Insulin bolus needs showed a decrease in the metformin group between V0 and V6 of -1.7 ± 5.7 units $(-5.5 \pm 16.8\%)$ and increased in the placebo group by 0.03 ± 6.0 units $(0.1 \pm 20.2\%)$, but the difference was not significant $(P = 0.059)$ (Table 2, Fig. 1). However, significant differences were noted in the metformin group at V2 and V4 compared with V0 (Table 2). Bolus doses at V6 were not different between the metformin and placebo groups $(0.38 \pm 0.12$ vs. 0.45 ± 0.17 units $\cdot kg^{-1} \cdot day^{-1})$.

A total of 7 of 31 patients (23%) treated with metformin and none of 31 patients (0%) treated with placebo were considered therapy responders, as defined by HbA_{1c} stability or improvement, at least a 20% reduction in insulin requirement, and no severe hypoglycemic episodes $(P = 0.001)$. Clinical and biological characteristics were not significantly different between responders and the other study subjects, but the treatment effect seemed better (but not significantly) in the youngest patients $(\leq 40$ years of age) with highest HbA_{1c} levels $(>7.5\%)$ and lowest BMI $(<25$ kg/m$^2)$. A backward logistic regression was performed using response/nonresponse as the dependent variable and including treatment, age, sex, duration of diabetes, BMI, HbA_{1c}, and fasting glycemia as independent variables, to detect predictor factors of response rate. We found that only treatment effect was highly significant $(P < 0.001)$, whereas BMI was close to significant $(P = 0.086)$.

Blood glucose control

HbA_{1c}. HbA_{1c} levels remained unchanged during the placebo run-in period in the placebo group $(7.38 \pm 0.75$ vs. $7.57 \pm 0.76\%$, NS) and in the metformin group $(7.40 \pm 0.67$ vs. $7.58 \pm 0.84\%$, NS); they also remained unchanged in the metformin and placebo groups between V0 and V6, although there was a trend of diminution between V0 and V2 in the metformin group $(7.58 \pm 0.84$ vs. $7.23 \pm 0.79\%$, $P = 0.07)$. After 6 months of treatment, HbA_{1c} was not different between the metformin and placebo groups $(7.45 \pm 0.78$ vs. $7.46 \pm 0.60\%$, respectively) and was not different from that at randomization for the both groups.

Means and SDs of SMBG. The mean number of SMBG estimations performed

Table 1—*Clinical and biological characteristics of the patients at randomization*

	Placebo (n = 31)	Metformin (n = 31)	P
Age (years)	41.1 ± 9.8	39.9 ± 12.9	NS
Sex (men/women)	20/11	17/14	NS
Weight (kg)	74.5 ± 11.7	78.4 ± 18.1	NS
BMI (kg/m^2)	25.8 ± 3.6	26.4 ± 4.6	NS
Systolic blood pressure (mmHg)	127 ± 11	133 ± 21	NS
Diastolic blood pressure (mmHg)	77 ± 9	81 ± 14	NS
Diabetes duration (years)	21.6 ± 10.2	16.9 ± 8.9	NS
CSII duration (years)	3.2 ± 3.1	4.5 ± 3.5	NS
Total insulin dose (units $\cdot$ kg^{-1} $\cdot$ day^{-1})	0.73 ± 0.22	0.72 ± 0.21	NS
Basal insulin rate (units $\cdot$ kg^{-1} $\cdot$ day^{-1})	0.28 ± 0.09	0.30 ± 0.15	NS
Bolus insulin dose (units $\cdot$ kg^{-1} $\cdot$ day^{-1})	0.44 ± 0.16	0.42 ± 0.13	NS
HbA$_{1c}$ (%)	7.57 ± 0.76	7.58 ± 0.84	NS
Fasting blood glucose (mg/dl)	148 ± 72	135 ± 63	NS
Total cholesterol (mg/dl)	202 ± 32	201 ± 27	NS
HDL cholesterol (mg/dl)	56 ± 14	58 ± 17	NS
LDL cholesterol (mg/dl)	130 ± 29	125 ± 31	NS
Triglycerides (mg/dl)	73 ± 42	71 ± 41	NS
Serum creatinine (mg/dl)	1.19 ± 0.13	1.17 ± 0.14	NS

Data are means ± SD.

by the patients was not different between the metformin and placebo groups (4.18 ± 0.6 vs. 4.0 ± 0.7 SMBG/day, respectively), and the frequency of SMBG remained unchanged throughout the study. The mean daily fasting capillary blood glucose levels were not significantly different between V0 and V6 in either group or between the metformin and placebo groups. In regard to the preprandial blood glucose levels, the mean and SD levels during the period V4–V6 tended to be lower in the metformin group than in the placebo group, but the differences did not reach statistical significance ($P = 0.065$ and 0.061). We did observe, however, during the period V4–V6 that the mean postprandial blood glucose level was significantly lower in the metformin group than in the placebo group (162 ± 61 vs. 188 ± 31 mg/dl, $P = 0.037$); a similar trend was evident during the period V2–V4 (177 ± 44 vs. 195 ± 35 mg/dl, $P = 0.074$).

Hypoglycemic and ketoacidosis episodes. According to the SMBG measurements, the number of hypoglycemic events (<60 mg/dl) with or without clinical symptoms between V0 and V6 in the metformin group compared with the placebo group was 47.2 ± 26.8 vs. 45.1 ± 23.5 events $\cdot$ patient^{-1} $\cdot$ 6 months^{-1}, respectively (7.8 ± 4.5 vs. 7.5 ± 3.9 events $\cdot$ patient^{-1} $\cdot$ month^{-1}, NS). We analyzed the absolute frequency of hypoglycemic episodes for each period of the study, and also the relative frequency (expressed as the ratio between absolute frequency and the number of SMBG measurements recorded by the patient). However, these frequencies were not different between the two treatment groups, whatever time period was studied.

A total of 27 severe hypoglycemic ep-

isodes (19 in the metformin group, 8 in the placebo group) were detected and recorded by the 62 patients during the 6 months of the study, corresponding to an incidence of 87 per 100 patient-years. These 27 severe hypoglycemic episodes were experienced by 8 of the 62 (12.9%) type 1 diabetic patients, five patients (16.1%) on placebo treatment and three patients (9.6%) on metformin therapy, but the difference was not statistically significant.

No cases of diabetic ketoacidosis were observed throughout the study in the two treatment groups.

Other biological parameters
Significant reductions of total cholesterol (201 ± 27 vs. 185 ± 26 mg/dl, $P = 0.04$) and LDL cholesterol (125 ± 31 vs. 120 ± 23 mg/dl, $P = 0.05$) were observed in the metformin group between V0 and V6. At V6, total cholesterol was not different between the metformin and placebo groups. HDL cholesterol was reduced in the metformin group from V0 to V6 (58 ± 17 vs. 56 ± 18 mg/dl, $P = 0.04$); a slight but not significant increase in fasting plasma triglycerides was noted (71 ± 41 vs. 90 ± 48 mg/dl). At V6, fasting triglycerides were not different between both groups. There was no significant modification in the metformin group (V0 versus V6) for creatinine, weight, and systolic and diastolic blood pressures (data not shown), and no difference for these parameters at V6 was seen between both groups.

Safety
During the study, in three patients in the metformin group, minor digestive symptoms (abdominal pain, diarrhea) developed, causing interruption of the trial. No patients required hospitalization during the trial. Mild or moderate gastrointestinal adverse effects were also reported in another eight patients in the metformin

Table 2—*Insulin requirements: relative mean change since randomization V0*

	Daily total IR (%)		Daily basal IR (%)		Daily bolus IR (%)	
Period	P	M	P	M	P	M
V0–V2	2.6 ± 11.1	−7.4 ± 18.4*	4.8 ± 19.5	−4.3 ± 24	2.0 ± 16.3	−9.4 ± 14†
V2–V4	2.9 ± 11.6	−10.6 ± 18.3‡	7.2 ± 23	−9.2 ± 28.5*	1.3 ± 15.1	−9.7 ± 11†
V4–V6	2.8 ± 12.7	−7.6 ± 19*	8.8 ± 27.1	−7.4 ± 24.7*	0.1 ± 20.2	−5.1 ± 17.6
V0–V6	2.8 ± 12.7	−7.8 ± 18†	8.8 ± 27.1	−7.9 ± 23.8*	0.1 ± 20.2	−5.5 ± 16.8

Data are means ± SD. P, placebo; M, metformin. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ versus randomization V0.

group (seven patients with one adverse effect, one patient with two adverse effects) compared with only two patients in the placebo group ($P = 0.069$).

CONCLUSIONS — Use of metformin, along with insulin therapy, has been studied less frequently in type 1 than in type 2 diabetes, but insulin-sparing effects of metformin have been observed (10–12,18). Most of these studies have been small (11), were uncontrolled (12), or were cross-over trials of short duration (10). Even in one previous trial involving the administration of insulin by CSII, the duration of treatment was only 3 weeks (19), and during this period, IR was not modified. Pagano et al. (10) showed the most marked reduction in IR in type 1 diabetic patients using large doses of metformin (850 mg three times a day). However, the 25% reduction in IR observed during 24-h euglycemic clamp did not really correspond to insulin needs in clinical practice.

In our study, we selected type 1 diabetic patients treated by CSII because this therapy allows differentiation of basal and prandial needs of insulin. We found a reduction in the basal rate of IR and, consequently, a reduction in total daily IR when metformin was added. To our knowledge, our study is the first to investigate the effect of adding metformin to insulin therapy in type 1 diabetes in a controlled, randomized, double-blind trial for such a long duration, which is the probable explanation for the differences observed between this and previous studies. In our study, the maximum effect of metformin in reducing IR was not seen until after 4 months of treatment, followed thereafter by a stabilization period. In contrast, previous studies showed that the insulin-sparing effect in type 1 diabetes occurred after a few days (20) or a few weeks of metformin use (10,12).

Although studies concerning multiple daily injections or CSII in type 1 diabetes have shown that metformin could reduce the increase in postprandial blood glucose by increasing insulin binding to its receptor (10,11,19), we did not find any significant reduction in bolus requirements after 6 months of treatment, although they did decrease significantly after 2 and 4 months in patients in the metformin group as compared with those given placebo. One explanation for this could be the ability of metformin to de-

crease fasting insulin resistance of type 1 diabetic patients that has been previously demonstrated using the euglycemic-hyperinsulinemic clamp procedure (21). This effect of metformin could be mediated by an increase of insulin-mediated glucose transport via GLUT1 and/or GLUT3 transporters (22) and/or an inhibitory action of metformin on gluconeogenesis (23) due to a primary inhibition of hepatic lactate uptake (24,25). Recently, in Sprague-Dawley rats, two mechanisms have been proposed to explain metformin action: inhibition of hepatic glucose phosphatase activity promoting glycogen sparing (26) and AMP-protein kinase activation, which could provide an explanation for the pleiotropic action of this drug (27). Another possibility could be the capacity of metformin to improve glucose-mediated glucose transport (28), which is the ability of glucose itself to promote glucose utilization (mass action effect of glucose). In type 1 diabetes, glucose-mediated glucose transport is impaired. Comparing these results with those of acarbose used in type 1 diabetes (29), metformin demonstrates a more pronounced insulin-sparing effect. To our knowledge, only one study using thiazolidinediones has been performed in patients with type 2 diabetes treated by CSII (9), but no data are available on use of this drug in type 1 diabetes.

In regard to glucose stability, as assessed by SMBG monitoring, we found a significant decrease in postprandial blood glucose level during the last period of follow-up in the metformin group. At the opposite end of the spectrum, we found no difference in fasting glycemia between the two treatments. Currently, there is no evidence of a protective effect of a decrease in blood glucose variability in regard to diabetic complications. However, as suggested by authors in the DCCT (30), mean HbA_{1c} is not the most complete expression of the degree of glycemia. In the DCCT, development of diabetic retinopathy was only partly explained by total glycemic exposure (mean HbA_{1c} × time of follow-up). The risk of such complications may be more dependent on the extent of postprandial hyperglycemia (31) and/or of glycemic excursions (32), which are not reflected by HbA_{1c} levels.

In the metformin group, the incidence of hypoglycemia <60 mg/dl was not different from that seen in the placebo group, and this incidence was close to

that reported in other studies (4,5). The frequency of severe hypoglycemia in our population of patients treated by CSII is of the same order of magnitude reported in the CSII group (81 per 100 patient-years) of the DCCT cohort (33).

No difference in weight change was found in our study. This is not surprising, because most of our patients had been treated with insulin for >15 years, and previous studies in type 1 diabetes (12) showed similar results. This is in contrast to the reduction of weight commonly observed in overweight type 2 diabetic patients treated by insulin therapy and metformin.

Metformin treatment was associated with a decrease in total cholesterol, related to the decrease in LDL cholesterol. HDL cholesterol was also slightly decreased and fasting plasma triglyceride levels were surprisingly increased in the metformin group, but the values still remained in the normal range. These results are different from those of previous studies performed in type 1 diabetic patients (12,21).

On an intention-to-treat basis, the success of a therapy depends on the absence of adverse effects. In this particular trial, the main end point was the benefit observed in terms of IR: not only did IR have to be reduced, but blood glucose levels had to be controlled and no hypoglycemic episodes had to have occurred. A total of 23% of the patients in the metformin group and no patients in the placebo group were considered to have had successful therapy. Therefore, we can conclude that additional therapy using metformin can be justified in type 1 diabetic patients treated by external pump with important basal insulin needs.

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