

Metformin Reduces Insulin Requirement in Type 1 (Insulin-Dependent) Diabetes

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Summary. The effect of metformin on Type 1 (insulin-dependent) diabetes has been assessed with the artificial pancreas. Fourteen Type 1 diabetic patients of normal body weight received in addition to their usual insulin therapy 850 mg metformin or placebo three times a day for 4–6 weeks. The sequence was placebo-metformin in eight patients and metformin-placebo in the other six. On the last day of metformin or placebo treatment, an artificial pancreas was used for about 36 h to assess insulin requirement. There was a 25.8% reduction in insulin requirement during metformin management despite slightly lower blood glucose levels (5.25 ± 0.20 versus 5.98 ± 0.18 mmol/l, $p < 0.01$). Maximum reduction (about 50%) occurred 2 h after both lunch and dinner. There was no nocturnal effect. A marked decrease in specific insulin binding before metformin was found ($0.56 \pm 0.27\%$ to 10^7 monocytes versus 2.82 ± 0.75 of control subjects) and significant in-

crease after metformin ($1.36 \pm 0.36\%$, $p < 0.05$). There were no significant changes in blood lactate, total and HDL-cholesterol, triglycerides and C-peptide levels.

These results show that insulin receptor binding is diminished in Type 1 diabetes, perhaps as a consequence of higher peripheral blood insulin levels and that metformin can improve binding, and so reduce the amount of insulin needed to reach euglycaemia. The insulin sparing effect is greatest after meals, and interference with intestinal absorption of sugars may also be important. It follows that metformin could be usefully administered to Type 1 diabetic patients with unimpaired liver and renal function to reduce their insulin requirement.

Key words: Type 1 diabetes, biguanides, metformin, insulin receptors, insulin therapy, artificial pancreas, Biostator.

Biguanides lower blood glucose concentration, although in practical terms their effect is only evident in diabetes mellitus [1]. The underlying mechanism is not fully understood, but support for a peripheral action has been shown recently by an enhancement of insulin receptors in the presence of phenformin [2] and metformin [3]. Studies *in vitro* [2, 3] have shown a rapid dose-dependent effect of biguanides on insulin binding to target cells, unrelated to changes in blood glucose or insulin concentration as in the case of other drugs [3]. This direct effect offers a more logical basis for earlier work showing sufficient potentiation of the peripheral [4] and hepatic effect to justify the use of biguanides in the treatment of Type 1 (insulin-dependent) diabetes mellitus. The combination of a biguanide with conventional insulin treatment in Type 1 diabetes, therefore, is an attractive possibility for many reasons, including the induced malabsorption of glucose [5] and other hexoses [6] and the possible control of secondary insulin-resistance.

The effectiveness of combined biguanide-insulin therapy in experimental animals [6] and in man [7] has hitherto been based on qualitative rather than quantitative evidence. The aim of the present work was to test the hypothesis that combined biguanide-insulin therapy may be usefully employed in Type 1 diabetic patients. The artificial endocrine pancreas was used to evaluate the insulin requirement over 24 h sedentary life in the presence or absence of metformin. The positive results of the acute administration of metformin in Type 1 diabetes have been reported recently [8].

Subjects and Methods

Subjects

All Type 1 diabetic patients under 60 years of age, with normal liver and kidney function, attending our outpatients clinic, were invited to take part in this 6-month study. Fifteen gave informed consent, of whom one dropped out after the first artificial pancreas session. Four-

Table 1. Data for the 14 patients at the end of the control period without metformin

Patients	Age (years)	Sex	Duration of diabetes (years)	Ideal body weight (%)	Insulin dose during the last 2 months (U/day)	HbA _{1(a+b+c)} (%)
Placebo-metformin						
1	52	M	22	+10	75	10.8
2	57	M	5	+7	58	10.4
3	60	M	20	+7	36	8.7
4	36	M	3	-5	75	7.4
5	31	M	4	+4	44	9.2
6	45	F	2	+3	56	10.7
7	47	M	5	+12	35	10.1
8	31	F	6	-13	45	9.9
Metformin-placebo						
9	35	M	5	-9	62	9.6
10	48	M	3	+12	42	10.8
11	43	M	8	+7	70	9.8
12	48	M	5	+4	44	10.0
13	27	M	16	-3	50	8.9
14	48	M	2	+6	35	7.5
Mean ± SEM	43.4 ± 2.7		7.6 ± 1.8		51.9 ± 3.9	9.6 ± 0.3

teen adult Type 1 diabetic patients were studied (12 male, 2 female; mean age 43 ± 3 years [SEM]; within +12% and -13% ideal body weight). They had been receiving insulin for 2–22 years, and, at the beginning of the experiment, were in fair metabolic control (glycosylated stable haemoglobin A_{1(a+b+c)} $9.56 \pm 0.30\%$). Their liver and kidney function was normal (liver enzymes and protein electrophoresis in the normal range, blood creatinine $< 110 \mu\text{mol/l}$, normal urinalysis). They showed no residual B cell function, as assessed by plasma C-peptide determination ($0.64 \pm 0.06 \text{ mmol/l}$ 20 min after 1 mg IV glucagon). Diet, physical activity and insulin dose ($51.9 \pm 3.86 \text{ U/day}$) remained unchanged throughout the study (Table 1).

Methods

Metformin 850 mg (Glucophage, Spemsa Florence, Italy) or a placebo was given three times a day before the main meals for 4–6 weeks. Placebo was given before metformin in eight patients, and metformin after placebo in the other six. At the end of placebo or metformin treatment, patients were subjected to artificial pancreas control (Biostator, Miles Laboratories, Elkhart Indiana, USA) to determine insulin requirement during a 3-day hospitalisation, during which automatic IV management ran from 19.00 h on day 1 to 07.00 h on day 3. The static plus dynamic control mode (3:1) was used for insulin administration. The preselected constants were: KF (a constant for falling glucose levels) = 166; BI (the preselected 'basal' level of glucose at which the basal insulin infusion rate is administered = 4.4 mmol/l); QI (the inverse for the static gain for insulin infusion) = 30; RI (the basal insulin infusion rate at the preselected 'basal' glucose level) = $0.05 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. No account was taken of the insulin requirement for the first 12 h (19.00–07.00 h), which was used as equilibration period. Meals were given at 07.00 h (300 kcal), 11.30 h (700 kcal) and 17.30 h (700 kcal). The composition of meals in both metformin and placebo treatments was the same: 50% carbohydrates, 30% fats and 20% proteins.

At 06.30 h on day 2 of Biostator application, venous blood was withdrawn from an antecubital vein during Biostator-induced euglycaemia after an overnight fast for the following determinations: lactate [9], total and HDL cholesterol [10], triglycerides [11]. The sensitivity and coefficients of variation for each assay in our laboratory are as follows: glycaemia 0.10 mmol/l , 2.5%; lactate 0.10 mmol/l , 4.8%; cholesterol 0.15 mmol/l , 5.1%; triglycerides 0.12 mmol/l , 6.2%; C-peptide 0.03 mmol/l , 6.6%; HbA_{1(a+b+c)} 0.1%, 3.4%. At the same time,

20 ml blood was collected from the antecubital vein to provide monocytes for insulin binding. Cells were isolated by gradient centrifugation according to Böyum [13] and suspended in Hepes buffer (100 mmol/l , pH 8) at a concentration of $10^7/\text{ml}$ monocytes, in the presence of $1 \text{ ng } ^{125}\text{I}$ -moniodoinsulin ($50\text{--}80 \mu\text{C}/\mu\text{g}$) prepared in our laboratory [14] and $100 \mu\text{g/ml}$ native insulin to determine the specific hormonal binding. Incubation was performed for 100 min at 15°C , and cells were separated according to Beck-Nielsen et al. [15]. Results are expressed as a percentage of specific binding of the total amount of insulin present in the medium. This measurement was carried out in five diabetic patients and in six well-matched healthy subjects.

Results

Metformin treatment was well tolerated by all patients, although most had transient abdominal pain and nausea for the first week of therapy.

Table 2 shows the amount of insulin administered by the Biostator for 24 h during placebo-metformin sequence (patients 1–8) and metformin-placebo sequence (patients 9–14). It can be seen that a requirement of $70.9 \pm 8.4 \text{ U/day}$ in the absence of metformin is replaced by a value of $51.7 \pm 6.18 \text{ U/day}$. This corresponds to a reduction of 25.8% ($p < 0.001$). Mean plasma glucose values were slightly lower after metformin therapy ($5.9 \pm 0.18 \text{ mmol/l}$ after placebo and $5.3 \pm 0.17 \text{ mmol/l}$ after metformin). Comparison between the two sequences made it clear that metformin did not have a sequence-effect. In subsequent calculations, therefore, the results were no longer referred to their sequence.

The hourly insulin requirement is illustrated in Figure 1. Mean 30 min plasma glucose values during Biostator application are shown: less insulin was administered by the Biostator during treatment with metformin.

Table 2. Daily insulin requirement determined by the artificial pancreas on the last day of treatment with placebo or metformin following overnight stabilization. The placebo-metformin sequence was followed in cases 1-8, the metformin-placebo sequence in cases 9-14

Patient	Insulin administered by artificial pancreas (U/24 h)		Variation (%)	Blood glucose during 24 h artificial pancreas application ^a (mmol/l)	
	After placebo	After metformin		After placebo	After metformin
1	133.69	105.22	-21.3	6.4	6.6
2	89.23	41.98	-52.9	5.9	4.7
3	42.53	31.51	-25.9	6.8	4.5
4	71.84	47.88	-33.3	5.7	5.1
5	57.12	41.75	-26.9	5.4	4.5
6	86.77	72.21	-16.7	6.5	6.6
7	33.51	23.04	-31.2	5.3	4.7
8	29.30	22.42	-24.5	4.9	4.4
9	78.25	67.35	-13.9	5.9	6.0
10	119.89	71.17	-40.6	6.9	5.5
11	93.96	70.58	-24.9	6.3	5.8
12	59.70	53.38	-10.6	6.3	4.7
13	54.88	35.59	-35.1	5.4	5.0
14	42.12	39.93	- 5.2	4.7	5.1
Mean ± SEM	70.91 ± 8.40	57.71 ± 6.18	25.8 ± 3.3	5.88 ± 0.18	5.25 ± 0.20

^a Blood glucose values are the mean of 1,440 determinations per patient

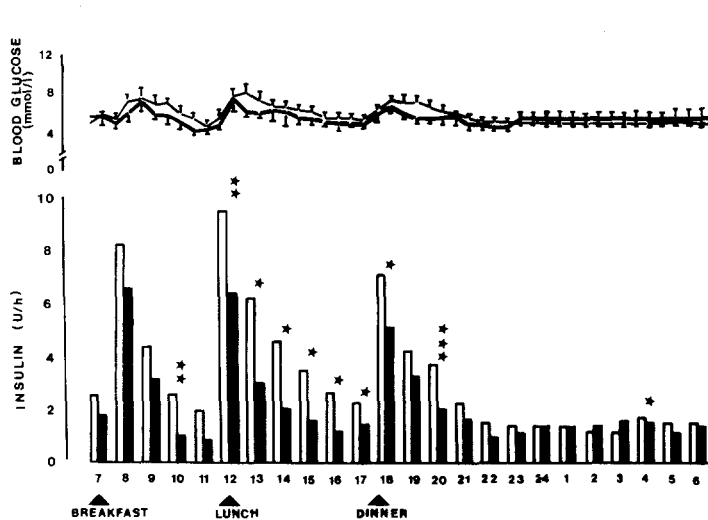


Fig. 1. Mean blood glucose levels are plotted every 30 min during control with (thick line) and without (thin line) metformin. Insulin administered is plotted hourly for day 2 on the artificial pancreas. □ without metformin. ■ with metformin. **p* < 0.05 ***p* < 0.01 ****p* < 0.005

In addition, the most significant differences were noted after meals: 50% reduction 2 h after lunch and dinner, respectively.

Changes in other plasma values are not significant: lactate concentrations varied from 1.1 ± 0.08 to 1.1 ± 0.07 mmol/l; total cholesterol concentrations from 4.7 ± 0.25 to 4.7 ± 0.26 mmol/l; HDL cholesterol from 1.15 ± 0.07 to 1.26 ± 0.6 mmol/l; triglycerides from 1.14 ± 0.10 to 1.18 ± 0.15 mmol/l.

Symptomatic hypoglycaemia needed a stable reduction in insulin administration as the study perceived in patients 2, 4 and 10.

Means and individual insulin binding values in five diabetic patients and the six control subjects are given

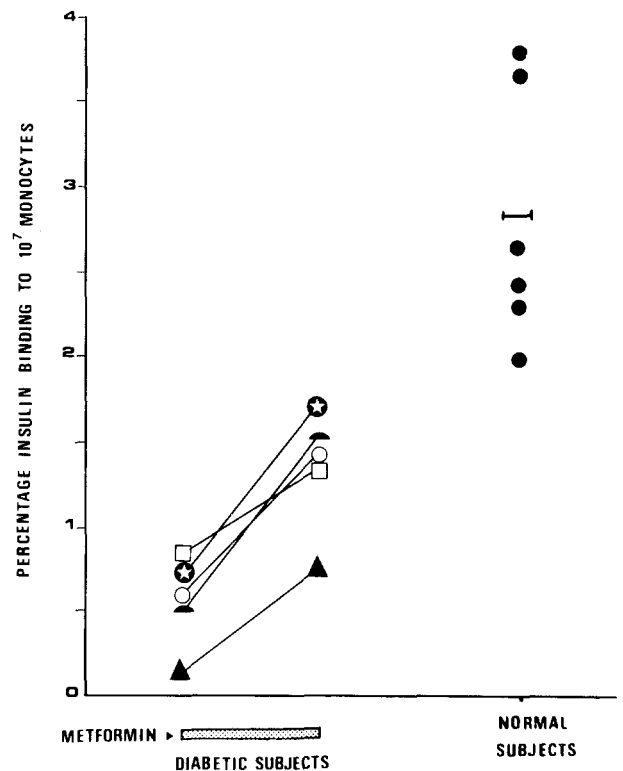


Fig. 2. Specific binding of ¹²⁵I-monoiodoinsulin to 10⁷ monocytes from 20 ml blood from five Type 1 diabetic patients and six well matched control subjects. The aspecific binding was subtracted by repeating the incubation in the presence or absence of 100 µg/ml cold insulin according to Beck-Nielsen et al. [15]. The second value was taken 4-6 weeks after the addition of metformin to the insulin treatment. Bar represents the mean value.

in Figure 2. The binding was well down in Type 1 diabetes, but rose to near the lower end of normal range after metformin. This increase was significant (*p* < 0.05), though the difference between it and normal levels was even more so (*p* < 0.001).

Discussion

Peripheral hyperinsulinism may lead to down-regulation of insulin receptors [16] and thus make Type 1 diabetic patients less sensitive to the action of the exogenous hormone. Metformin improves insulin binding to target cells in vitro [2, 3] and might be expected to improve insulin sensitivity in Type 1 diabetic patients. Insulin binding to monocytes in our series was significantly lower than in normal subjects, and metformin treatment increased the number of insulin receptors on monocytes. These results agree with reports in vitro [2, 3] and in vivo [17] and give a rationale for the use of metformin in association with insulin treatment. Our results show that this approach is of practical value since there was a 25.8% decrease in daily insulin requirement after metformin. This reduction in insulin requirement is probably under-estimated owing to the slightly lower blood glucose values during metformin treatment. In five subjects there was a 39% increase in insulin binding to isolated monocytes after 4–6 weeks of metformin treatment, in agreement with results in vitro [2, 3]. This may well be a fundamental mechanism of the action of biguanides in diabetes.

A supplementary mechanism is suggested by the observation that a maximum reduction in insulin requirement took place after the two main meals. This is in line with the view that metformin alters the intestinal absorption of carbohydrates. It would also explain the absence of a nocturnal effect, though it should not be forgotten that the drug has a half-life of 3–5 h [18].

None of our patients displayed significant evidence of hyperlactataemia, indicating that this occurs mostly in patients with liver and renal failure [19] and is very rare when metformin is used [19]. By contrast with non-insulin-dependent diabetes [20], there was no significant change in blood cholesterol and triglycerides.

Our overall conclusion is that metformin can be administered to Type 1 diabetic patients with unimpaired liver and renal function without risk of hyperlactataemia. Its benefits include improved glycaemic control and a significant reduction in insulin requirement. Effects of this kind have been predicted in the past [7]. Their existence can now be demonstrated and gives support to the view that metformin acts directly on insulin receptors.

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