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Combined Pioglitazone and Metformin Treatment Maintains the Beneficial Effect of Short-Term Insulin Infusion in Patients with Type 2 Diabetes: Results from a Pilot Study

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Abstract

Background:

The aim of our study was to examine the efficacy of short-term intravenous insulin intervention followed by oral pioglitazone/metformin therapy to prevent patients from continuous insulin application.

Methods:

This prospective, open-label, 4-month pilot study comprised of 14 diabetes patients (5 female, 9 male; age 60 ± 2 years; body mass index 29 ± 3.2 kg/m²; hemoglobin A1c [HbA1c] 7.6 ± 1.1%) with (1) insufficient glycemic control under a dose of metformin ≥1700 mg/day and/or metformin plus additional oral antidiabetes drugs (OADs) and (2) appropriate residual β-cell function. Initially, an inpatient 34 h continuous intravenous insulin infusion was performed, and metformin was given (2x 850 mg/day). Insulin was stopped, and pioglitazone 30 mg/day was added at the second inpatient day. Patients were followed for four months. Efficacy parameters [change of HbA1c, fasting blood glucose [FBG], intact proinsulin, adiponectin, and high-sensitivity C-reactive protein (hsCRP)] were assessed after initial normalization of blood glucose values by intravenous insulin and at the study end point.

Results:

During the acute insulin intervention, FBG levels were stabilized in all study subjects. In the following OAD treatment period, five patients showed an improvement of HbA1c > 0.5% [35.7%; seven patients remained stable (50.0%), two patients were nonresponders (14.3%)].

continued →

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Abbreviations: (FBG) fasting blood glucose, (HbA1c) hemoglobin A1c, (HOMA-IR) homeostasis model assessment of insulin resistance, (hsCRP) high-sensitivity C-reactive protein, (NS) not significant, (OAD) oral antidiabetes drug, (PPARγ) peroxisome proliferator-activated receptor γ, (T2DM) type 2 diabetes mellitus

Keywords: cardiovascular risk, glycemic control, pioglitazone, type 2 diabetes

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Abstract cont.

Fasting glucose values dropped after insulin infusion (-17.7%; $p < .001$). This effect was maintained during the consecutive OAD treatment period (glucose +0.3%, not significant (NS); HbA1c -6.0%; $p < .05$). The initial decrease in fasting intact proinsulin levels was also maintained during the study (end value -41%, $p < .05$).

Improvements in hsCRP values (postinsulin value, -15%, NS; end value -37%; $p < .05$) and adiponectin values (postinsulin value +15%, NS; end value +128%; $p < .001$) were demonstrated at end point only after continued glitazone intake.

Conclusions:

Our pilot study demonstrated that a beneficial effect of a short-term intravenous insulin application on glycemic control was effectively maintained by pioglitazone/metformin treatment for at least 4 months. In addition, the oral therapy significantly improved cardiovascular risk parameters.

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Introduction

Glycemic control is mandatory for the prevention and treatment of vascular complications in patients suffering from type 2 diabetes mellitus (T2DM). When pharmacological intervention with oral antidiabetes drugs (OADs) is insufficient to achieve adequate metabolic control, subcutaneous insulin therapy is usually introduced. In cases of deteriorated T2DM, acute intervention with intravenous insulin application seems to be the best therapeutic strategy to achieve an immediate reduction in blood glucose levels.[1] Nevertheless, there is little evidence that these patients need to stay on insulin treatment forever. It is tempting to speculate that a patient can be subsequently treated with OADs once stable euglycemia is achieved by short-term insulin intervention.[2]

The possibility of such an insulin-induced disease remission is supported by a study from Weng and colleagues, who treated newly diagnosed patients with T2DM for 3 weeks to strict normality with either an oral antidiabetes therapy (sulfonylurea and metformin), intensive insulin injection therapy, or a continuous subcutaneous insulin infusion treatment with insulin pumps, respectively.[3] After the end of this intensive therapy, they treated the patients for one year with diet and exercise only. An oral glucose tolerance test, performed to investigate the diabetes status after 12 months, revealed that the majority of previously orally treated patients had regained the disease, while the vast majority of previously insulin treated patients was still non-diabetic, with a slightly more pronounced effect by the insulin pump therapy.[3]

Pioglitazone, an antidiabetes drug with insulin-sensitizing effects, is a candidate for a successful treatment continuation after initial insulin intervention without insulin. Besides its glucose-lowering property by reducing insulin resistance in the liver and peripheral tissues, the peroxisome proliferator-activated receptor γ (PPARγ) agonist pioglitazone exerts beneficial effects on the dyslipidemic and chronic inflammatory conditions observed in diabetes patients.[4]

The goal of this pilot study was to investigate whether the effect of a 34 h intravenous insulin infusion on the metabolic control in T2DM patients with inadequate disease control with OAD therapy can be successfully maintained by subsequent combined pioglitazone/metformin treatment. We investigated the change of the hemoglobin A1c (HbA1c) value over an observation interval of 4 months for efficacy assessment. Further secondary parameters associated with an increased cardiovascular risk such as the dyslipidemic and chronic inflammatory status were examined (1) after initial blood glucose stabilization achieved by the short-term intravenous insulin intervention and (2) with subsequent treatment by pioglitazone/metformin. Such a treatment option may, e.g., be reasonable for hospitalized or immobile patients with (moderately) deteriorated T2DM

who wish to remain on OADs instead of subcutaneously applied insulin for further treatment.

Material and Methods

Study Design

This single-center, prospective, open-label pilot study was approved by the responsible Ethics Committee of Rhineland-Palatinate, Mainz, Germany. A written informed consent prior to any study procedure was mandatory for participation in this trial.

Type 2 diabetes patients were considered eligible to participate in this trial when meeting the following inclusion criteria: (1) age 30–75 years, (2) treatment with a maximal dose of metformin (≥1700 mg/day) or a combination of metformin and at least one additional oral antidiabetes drug, (3) more than two fasting or postprandial blood glucose measurements >200 mg/dl within the past two weeks, (4) current HbA1c value ≥6.5%, and (5) an appropriate residual β-cell function assessed by a fasting C-peptide level >2 ng/ml (lower laboratory reference value for normal β-cell function).

Major exclusion criteria were type 1 diabetes mellitus (GAD-antibody positive, fasting C-peptide <0.6 ng/ml), pretreatment with PPARγ agonists within 3 months, acute severe infections, treatment with nonsteroidal antirheumatics, use of systemic corticosteroids within the past 3 months, history of ketoacidosis or lactate acidosis, more than one unexplained episode of severe hypoglycemia within 6 months, heart failure or respiratory insufficiency, history of myocardial infarction within the past 6 months, and history of significant cardiovascular (NYHA stage II–IV), respiratory, gastrointestinal, hepatic (alanine aminotransferase and/or aspartate aminotransferase >2.5 times the normal reference range), renal (creatinine >1.1 mg/dl in women and >1.5 mg/dl in men), neurological, psychiatric and/or hematological disease.

The percentage of patients whose HbA1c improved after pioglitazone/metformin treatment following stabilization of glycemic control was the primary efficacy parameter (HbA1c improvement by at least 0.5 percentage points after 4 months as compared to baseline). The secondary efficacy parameters consisted of fasting blood glucose (FBG), mean change in HbA1c, intact proinsulin, adiponectin, and high-sensitivity C-reactive protein (hsCRP).

Study Performance

After baseline blood drawings, 14 patients were treated in three subsequent inpatient days to ensure optimized glycemic control. A 34 h continuous intravenous regular human insulin infusion (Huminsulin, ELI Lilly) was initiated in the morning of the first day to stabilize the blood glucose level of the patient within the range of 80 mg/dl (fasting) to 160 mg/dl (postprandially). The insulin infusion started with a dose of 1 U/h and was individually adjusted to avoid a drop in blood glucose by more than 50 mg/dl within 3 h. Metformin was given in a dosage of 850 mg twice daily before breakfast and dinner from the morning of the first inpatient day onward. Additional pioglitazone intake of 30 mg once daily before breakfast was started at the second inpatient day. After termination of the insulin infusions in the evening of the second day, blood was drawn in the morning of the third inpatient day for measurement of the secondary efficacy parameters.

Under continued combined oral pioglitazone/metformin treatment for the next 4 months, FBG values and safety parameters were assessed at three interval visits.

Laboratory Procedures

Hemoglobin A1c was measured by an automated reversed-phase cation exchange gradient chromatography (AdamsTM A1c, A. Menarini Diagnostics). For all other parameters, serum and plasma samples were stored at -80 °C until determination at the end of the study. Plasma glucose was determined by an enzymatic-amperometric measuring principle (SuperGL, Dr. Mueller Geraetebau); insulin was quantified using a two-site immunochemiluminometric assay (Invitron) while adiponectin was measured with a radioimmunoassay (Linco/Millipore). High-sensitivity C-reactive protein was determined immunoturbidimetrically (Falcor 350, A. Menarini Diagnostics). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from the fasting insulin and glucose values by means of the homeostasis model assessment analysis (HOMA-IR score = insulin [mU/liter] x glucose [mmol/liter]/22.5),[5] with values >2 classified as insulin resistant.[6]

Data Analysis

The statistical analyses was performed using the R software package Version 2.3.1 under the Microsoft Windows XP® Professional, Version 2002, Service Pack 2.

The mean values at baseline and end point of the efficacy variables were compared by Student's t test. Due to the pilot character of this trial, all p values and the corresponding confidence intervals of inferential statistical methods were interpreted in an exploratory sense. Significance levels of $p < .05$ were considered statistically significant.

Results

Out of 23 screened patients, 15 patients (8 patients did not meet the entire inclusion/exclusion criteria) were included in the study and were analyzed as intention-to-treat study cohort that thus consisted of overweight T2DM patients of Caucasian origin exclusively. One patient could not be controlled by intravenous insulin therapy in the initial inpatient period and did not participate in the consecutive oral follow-up procedures. **Table 1** summarizes the demographic data of the remaining 14 patients who form the per-protocol analysis set, the results of which are further reported in this article. Treatment compliance of the patients was calculated based on returned empty packages and was 97.6% ± 2.5% for pioglitazone and 96.6% ± 2.1% for metformin. The oral therapy was well tolerated, and no patient experienced a serious adverse event.

Comparisons of baseline efficacy parameter values, values after insulin intervention, and values at end of the study are given in **Table 2**.

The patients presented with an initial HbA1c value of 7.6% ± 0.8%. Euglycemia (consistent blood glucose levels <140 mg/dl) was achieved in all 14 patients of the per-protocol analysis set during the 34 h intravenous insulin infusion. After termination of the insulin application, FBG levels decreased from 171 ± 38 mg/dl at baseline to 137 ± 30 mg/dl at sampling in the next morning (i.e., at least 8 h after the last insulin dose), representing a reduction by 17.7% of the initial value. The primary

Table 1.
Demographic Data of the Study Cohort Stratified by Final Intervention Success (HbA1c Reduction)

Group	Patient number	Gender	Age (years)	Body mass index (kg/m^2)	Diabetes Duration (years)	Initial HbA1c (%)	End point HbA1c (%)	Pretreatment
HbA1c improvement > 0.5%	1	female	62	25.8	6	9.0	7.4	metformin
	5	male	57	32.8	2	8.4	6.5	metformin
	7	male	68	30.9	5	7.1	6.5	metformin
	8	male	66	28.7	16	8.4	7.3	metformin
	9	male	54	29.6	6	8.1	7.6	metformin + glibenclamide
HbA1c improvement 0–0.5%	2	male	64	30.8	11	7.1	6.7	metformin
	6	male	60	30.3	2	8.0	7.6	metformin
	10	female	55	28.5	10	6.8	6.4	metformin
	12	female	71	29.9	6	8.0	7.6	metformin + glimepiride
	13	female	62	37.9	5	6.8	6.4	metformin + repaglinide
	14	male	58	37.4	6	8.5	8.1	metformin
No change in HbA1c	3	female	59	30.5	8	6.8	6.8	metformin
HbA1c increase	4	male	67	30.7	4	6.9	7.0	metformin
	11	male	58	32.3	6	6.8	7.7	metformin + glimepiride + acarbose
Mean	—	—	60 ± 2	29 ± 3.2	6	7.6 ± 0.8	7.1 ± 0.6	—

Table 2.
Baseline Values and Variations of the Efficacy Parameters (Per-Protocol Set of 14 Patients)[a]

Observation period	Fasting glucose			HbA1c			HOMA-IR			Intact proinsulin			hsCRP			Adiponectin		
	(mg/dl)	%	*p* value	(%)	%	*p* value	Score	%	*p* value	(pmol/liter)	%	*p* value	(mg/liter)	%	*p* value	(µg/ml)	%	*p* value
Baseline to end point	171 ± 38 to 136 ± 25	20.2	.0002	7.61 ± 0.81 to 7.11 ± 0.56	6.0	.019	7.1 ± 5.1 to 3.4 ± 1.6	52.4	.003	17.8 ± 13.9 to 10.6 ± 8.1	40.6	.026	2.0 ± 1.7 to 1.3 ± 0.8	36.6	.043	8.5 ± 4.2 to 19.4 ± 8.4	128.0	<.0001
Baseline to postinsulin	171 ± 38 to 137 ± 30	17.7	.0004	—	—	—	7.1 ± 5.1 to 3.5 ± 1.8	53.9	.019	17.8 ± 13.9 to 9.5 ± 4.8	46.4	.007	2.0 ± 1.7 to 1.7 ± 1.3	15.4	.177	8.5 ± 4.2 to 9.8 ± 4.0	15.5	.094
Postinsulin to end point	137 ± 30 to 136 ± 25	0.3	.478	—	—	—	3.5 ± 1.8 to 3.4 ± 1.6	2.7	.423	9.5 ± 4.8 to 10.6 ± 8.1	-11.0	.771	1.7 ± 1.3 to 1.3 ± 0.8	25.2	.038	9.8 ± 4.0 to 19.4 ± 8.4	97.4	<.0001

[a] % = mean percentage of individual improvements; data are given as mean ± standard deviation.

end point (HbA1c reduction by more than 0.5%) was achieved in five patients (intent-to-treat population 33.3%, $p < .05$; per-protocol population 35.7%, $p < .01$). However, a numerical reduction in HbA1c from screening to end point could be observed in total in 11 of 14 study participants (78.6%; $p = .0236$, see **Table 2**). For one patient, no HbA1c change was observed, whereas in two patients the HbA1c value increased (nonresponders).

Significant improvements were also shown for the cardiovascular risk parameters, adiponectin and hsCRP, and intact proinsulin, a direct marker for β-cell functionality and indirect biomarker for insulin resistance and cardiovascular risk (**Table 2** and **Figure 1**).

Discussion

This study investigates the efficacy of a combined pioglitazone/metformin treatment to maintain the improvement in glycemic control achieved by short-term intravenous insulin infusion in patients with T2DM. Furthermore, the impact of oral pioglitazone/metformin therapy on metabolic circulatory parameters and cardiovascular risk markers is examined.

Short-term insulin infusion can be used as treatment strategy for decompensated T2DM. Nevertheless, acute intravenous insulin intervention alone does not demonstrate long-term effects in all patients, and the improvement of glycemic control is limited in the majority of responders to a period of three months or less.[2]

Our study cohort consisted of 14 overweight T2DM patients with chronic insulin resistance and increased fasting as well as mean blood glucose levels under pharmacological therapy with metformin alone or in combination with other OADs.

Immediate improvement of glycemic control was achieved after start of a continuous intravenous insulin infusion and was kept stable for 34 h in each patient. After termination of insulin intervention, FBG dropped to significantly lower glucose values in all patients (from 171 to 137 mg/dl). A 46% decrease in intact proinsulin values demonstrated a significant improvement of the β-cell function during the insulin infusion. Insulin resistance was lowered as demonstrated by significantly lowered HOMA-IR scores. These first-phase metabolic improvements can be attributed solely to the intravenous insulin administration.

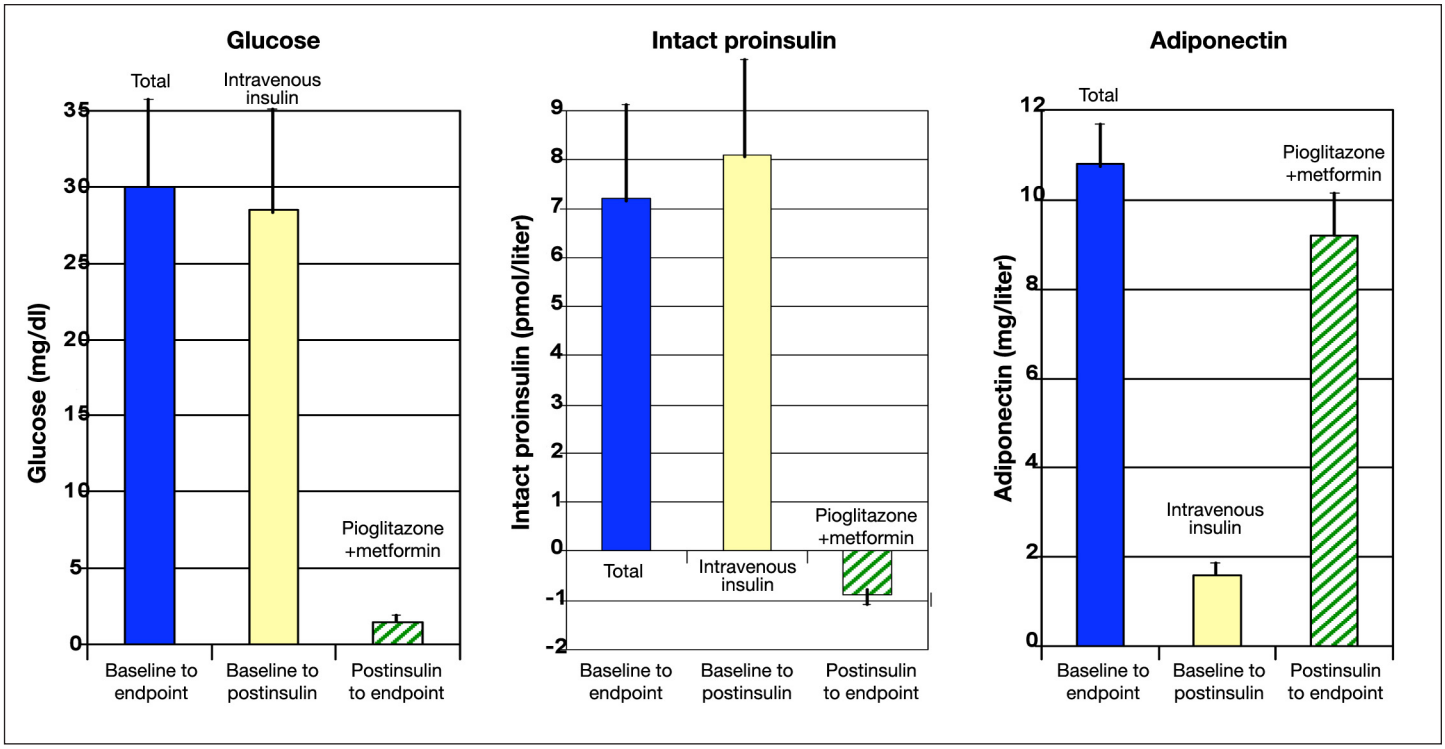

Figure 1. Effects of acute intravenous insulin intervention versus long-term pioglitazone + metformin treatment on glucose, intact proinsulin, and adiponectin concentrations. Values are given as differentials from the respective baseline values (mean ± standard deviation).

Pioglitazone increases the sensitivity of insulin on the insulin receptors and thus enhances the glucose uptake from the blood stream into adipocytes and skeletal muscle cells, in addition to repressing the glucose output from hepatocytes. It is well established that pioglitazone increasingly improves insulin sensitivity within the first months of treatment and reaches the full effect after approximately two months while the beneficial effect on metabolic markers can be demonstrated after as little as two weeks.[4,7–9]

A body of data is available showing the decrease of FBG after pioglitazone treatment alone[10–15] or in combination with other commonly used OADs such as sulfonylurea drugs[16,17] or metformin.[18,19] However, these studies have in common that the subjects started pioglitazone intake with high FBG values ranging from 146 mg/dl[15] to 279 mg/dl.[10] Successful therapy was assessed by mean change in FBG values ranging from -6.6%[13] to –21.9%[10] for pioglitazone monotherapy. For combination therapy, FBG improvements range from –13.9%[19] to –21.8%[16] with sulfonylurea and from –16.1%[19] to –23.0%[18] with metformin. No data are available showing the beneficial effects of pioglitazone when treatment starts with stabilized glucose levels. An immediate insulin intervention is considered appropriate to achieve this condition.

In our pilot study, addition of pioglitazone (30 mg/day) to the continued metformin therapy after the inpatient insulin treatment succeeded in maintaining the improved glycemic control achieved by the insulin intervention for 4 months in most patients (except for two nonresponders). This was demonstrated by (1) a further decrease of HbA1c of up to 0.5% in seven patients (50%) and of more than 0.5% in five patients (36%) and (2) by a highly significant improvement of the fasting glucose levels.

Insulin resistance as measured by HOMA-IR was not lowered further during the OAD treatment period but was maintained at the low level achieved by the initial insulin infusion. In an analogous Austrian two-arm study on poorly insulin-treated patients with T2DM, the insulin requirement of the pioglitazone-treated group (15 mg/day) was significantly reduced compared to the control group who underwent short-term insulin infusion without additional treatment with an insulin sensitizer.[2]

It is well-known that pioglitazone exerts additional beneficial effects on surrogate markers of cardiovascular risk and pancreatic β-cell protection[20] beyond its effects on glucose metabolism. Proinsulin is synthesized by the β cell of the pancreas as a precursor molecule for insulin. Physiologically, virtually all proinsulin molecules are intracellularly cleaved into insulin and C-peptide. In healthy subjects, only a minor percentage of uncleaved intact proinsulin is (postprandially) released into the circulation. An insufficient cleavage capacity of the β cell for proinsulin to insulin—resulting from an increased insulin demand triggered by insulin resistance—leads to an increased secretion of intact proinsulin molecules.[21] Intact proinsulin is therefore a marker for secretory β-cell dysfunction, an indirect predictor of insulin resistance[22] and an independent cardiovascular risk factor due to stimulation of plasminogen activator inhibitor-1 secretion and inhibition of fibrinolysis.[21]

In our study, a beneficial 46% decrease of fasting intact proinsulin levels was observed after metabolic recompensation with intravenous insulin. This effect was maintained during the pioglitazone/metformin treatment, but the circulatory levels of fasting intact proinsulin did not improve further. This is congruent to the observation that postprandial but not fasting plasma levels of this insulin precursor drop during glitazone therapy; in nondiabetes patients at cardiovascular risk treated with pioglitazone for 4 months, unchanged fasting intact proinsulin levels were opposed by a significant reduction of the postprandial increase in intact proinsulin as measured during a standardized oral glucose load.[23]

In contrary to intact proinsulin, the cardiovascular risk marker adiponectin, which demonstrated no changes after the acute insulin intervention, continuously improved significantly during the pioglitazone/metformin treatment phase. The circulatory parameter adiponectin is a fat-derived hormone with cardioprotective properties that decreases with an increase of visceral fat depots.[24,25] Thus adiponectin elevation is one of the surrogate markers for success of an antidiabetes therapy.[15,26] In the study presented, adiponectin levels improved significantly in response to pioglitazone treatment at least by a factor of 2. A body of data is available showing that pioglitazone increases adiponectin plasma levels in T2DM patients.[15,27,28] The effect seems to be at least partly independent of glucose levels.[29] The generally accepted anti-inflammatory effects of pioglitazone may be mediated via restoration of hypoadiponectinemia.[30]

Another marker of vascular inflammation is hsCRP, which shows a linear correlation with cardiovascular risk in the range of 0–10 mg/dl[31] and is considered a valuable marker for cardiovascular risk assessments.[32,33] We here confirm that pioglitazone is able to highly significantly reduce hsCRP levels over a treatment

period of 4 months.[34–37] This effect appears to be a rapid physiologic reaction on PPARγ activation and can be observed within a short-term interval after starting a pioglitazone therapy.[37,38] We conclude that pioglitazone exerts additional beneficial effects on biomarkers of vascular inflammation independent from the initially performed short-term insulin intervention and therefore independent from the initial metabolic situation of the respective patient.

The major limitation of our pilot trial is the lack of a comparator group (e.g., metformin + sulfonylurea) in the oral postinsulin treatment group. Future studies should confirm these effects in comparison with other oral drug regimens.

In summary, this pilot study confirms that, in T2DM patients, the beneficial effect of a 34 h intravenous insulin infusion on glycemic control and cardiovascular risk markers can be successfully maintained by consecutive combined pioglitazone/metformin treatment over a period of at least 4 months.

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