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Pioglitazone improvement of fasting and postprandial hyperglycaemia in Mexican-American patients with Type 2 diabetes: a double tracer OGTT study

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Summary

Objectives—By using tracer techniques, we explored the metabolic mechanisms by which pioglitazone treatment for 16 weeks improves oral glucose tolerance in patients with type 2 diabetes when compared to subjects without diabetes.

Methods—In all subjects, before and after treatment, we measured rates of tissue glucose clearance (MCR), oral glucose appearance (RaO) and endogenous glucose production (EGP) during a (4-h) double tracer oral glucose tolerance test (OGTT) ($1\text{-}^{14}\text{C}$ -glucose orally and $3\text{-}^3\text{H}$ -glucose intravenously). Basal hepatic insulin resistance index (HepIR) was calculated as $\text{EGP} \times \text{FPI}$. β -cell function was assessed as the incremental ratio of insulin to glucose ($\Delta\text{I}/\Delta\text{G}$) during the OGTT.

Results—Pioglitazone decreased fasting plasma glucose concentration (10.5 ± 0.7 to 7.8 ± 0.6 mM, $P < 0.0003$) and HbA1c (9.7 ± 0.7 to $7.5 \pm 0.5\%$, $P < 0.003$) despite increased body weight and no change in plasma insulin concentrations. This was determined by a decrease both in fasting EGP (20.0 ± 1.1 to 17.3 ± 0.8 $\mu\text{mol/kg}_{\text{ffm}}$ min, $P < 0.005$) and HepIR (from 8194 declined by 49% to 3989, $P < 0.002$). During the OGTT, total glucose Ra during the 0- to 120-min time period following glucose ingestion decreased significantly because of a reduction in EGP. During the 0- to 240-min time period, pioglitazone caused only a modest increase in MCR ($P < 0.07$) but markedly increased $\Delta\text{I}/\Delta\text{G}$ ($P = 0.003$). The decrease in 2h-postprandial hyperglycaemia correlated closely with the increase in $\Delta\text{I}/\Delta\text{G}$ ($r = -0.76$, $P = 0.004$) and tissue clearance ($r = -0.74$, $P = 0.006$) and with the decrease in HepIR ($r = 0.62$, $P = 0.006$).

Conclusions—In diabetic subjects with poor glycaemic control, pioglitazone improves oral glucose tolerance mainly by enhancing the suppression of EGP and improving β -cell function.

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Competing interest/financial disclosure

Leonard C. Glass is currently employed by Lilly Research Laboratories. Ralph A. DeFronzo has received investigational grants and consulting honoraria from Takeda Pharmaceuticals North America. Eugenio Cersosimo is a member of the speaker bureau for Takeda America. Kenneth Cusi, Rachele Berria, Roberta Petz and Amalia Gastaldelli have nothing to declare. This work was supported in part by grants from Takeda Pharmaceuticals North America, National Institutes of Health Grant DK-24092, GCRC grant, and a Veterans Administration Merit Award. AG was partly supported by institutional grant from the Italian National Research Council (CNR) ME.P01.012.003.

Introduction

Individuals with type 2 diabetes mellitus are characterized by defects in insulin secretion and insulin sensitivity.^{1,2} Early in the natural history of type 2 diabetes, the insulin resistance is fully established, but glucose tolerance remains normal because of increased secretion of insulin by the pancreas.¹⁻³ With time, however, the beta cell begins to fail and overt glucose intolerance develops.¹⁻⁴ It is desirable, therefore, to have antidiabetic drugs that are capable of enhancing tissue sensitivity to insulin and improving beta cell function. The thiazolidinediones have been shown to improve glycaemic control and enhance muscle insulin sensitivity during euglycaemic insulin clamp studies.⁵⁻¹⁰ Although less well appreciated, we also have shown that the thiazolidinediones have an insulin-sensitizing effect on the liver.^{8,11} The oral glucose tolerance test (OGTT), especially if combined with tracer infusion, allows simultaneous evaluation of insulin secretion and insulin sensitivity (peripheral and hepatic). Thus, we examined the mechanisms via which thiazolidinediones improve glucose tolerance following glucose ingestion, i.e. the effect on peripheral and hepatic insulin sensitivity and beta cell function.

Following glucose ingestion, the plasma glucose concentration rises, insulin secretion is stimulated and the combination of hyperglycaemia plus hyperinsulinemia combines to: (i) suppress endogenous (primarily hepatic) glucose production (EGP); (ii) enhance tissue (primarily muscle) glucose disposal and (iii) augment splanchnic (liver plus gut tissues) glucose uptake. To examine which of these mechanisms are responsible for the improvement in glucose homeostasis following treatment with pioglitazone, in patients with type 2 diabetes, we performed an OGTT-double tracer study¹²⁻¹⁴ to quantify basal EGP, the rate of appearance of ingested glucose into the systemic circulation, suppression of EGP during the OGTT and whole body glucose disposal rate following ingestion of an oral glucose load.

Material and methods

Twenty-four Mexican-American subjects, 12 with type 2 diabetes mellitus (T2DM) (seven men and five women; age = 54 ± 2 ; BMI = 30.5 ± 1.1 kg/m², HbA1c = $9.7 \pm 0.7\%$, duration of diabetes 4 ± 1 years) and 12 with normal glucose tolerance (NGT) (four men and eight women, age = 42 ± 4 ; BMI = 30.4 ± 1.1 kg/m²), participated in the study. Five subjects with T2DM were taking a stable dose of sulfonylurea for at least 3 months before study, and seven subjects were treated with diet alone. Patients who had received insulin, metformin or another thiazolidinedione in the previous 12 months were excluded. No subject was taking any drug [except sulfonylureas (SU)] known to affect glucose metabolism. In the five subjects who were taking a sulfonylurea, the drug was continued.

Three weeks before the study, all subjects met with a dietitian and were instructed to consume a weight-maintaining diet containing 50% carbohydrate, 30% fat and 20% protein. In the five subjects who were taking a sulfonylurea, the drug was continued during the three weeks of diet. Sulfonylurea-treated subjects discontinued their medication 48 h before the study. As SU have no known direct insulin-sensitizing effects¹⁵ and because the results in sulfonylurea-treated and diet-treated groups were virtually identical, the two groups were combined for data analysis.

All subjects were in good general health without evidence of cardiac, hepatic, renal or other chronic diseases as determined by history, physical examination, screening blood tests, EKG and urinalysis. No subject participated in any heavy exercise before or during the study, and body weight was stable (± 1.5 kg) over the 6 months prior to study. All subjects gave signed voluntary informed consent before participation, and the protocol was approved by the

Institutional Review Board of the University of Texas Health Science Center at San Antonio.

Study design

On the day of the baseline (pre-pioglitazone), T2DM and NGT study subjects received baseline measurement of fasting plasma glucose and insulin concentrations (mean of three values drawn at -30, -15 and 0 min) and HbA1c twice. On the same day, a 4-h double tracer ($1\text{-}^{14}\text{C}$ -glucose orally and $3\text{-}^3\text{H}$ -glucose intravenously) – oral glucose (75 g) tolerance test (OGTT)^{12,13} was performed to evaluate overall glucose tolerance, insulin secretion, endogenous (hepatic) glucose production (EGP), rate of appearance of ingested glucose in the systemic circulation and tissue glucose clearance rate. All studies were initiated at 0500 h, following an overnight fast.

Following completion of these studies, T2DM subjects were started on pioglitazone, 45 mg/day, for 16 weeks. During the pioglitazone treatment period, subjects returned to the Clinical Research Center every 2 weeks at 0800 h, following an overnight fast, for measurement of fasting plasma glucose, body weight and blood pressure. Fasting plasma lipids (total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol) were measured monthly, and HbA1c was measured twice during the last week of pioglitazone treatment. On each visit, dietary adherence was reinforced. After 16 weeks of pioglitazone treatment, all subjects underwent a repeat double tracer OGTT.

In this study, five subjects with type 2 diabetes were allowed to continue use of their SU which have been shown to significantly increase proinsulin as well as the proinsulin to immunoreactive insulin ratios when compared with thiazolidenediones.¹⁶ Therefore, to minimize any potential effect of the SU on the day of testing, subjects were instructed to discontinue the use of SU 48 h prior to testing.¹⁷

OGTT-double tracer study

Subjects were admitted to the GCRC at 5 PM on the evening prior to the study and received a standardized diet containing 50% CHO, 30% fat and 20% protein. They were not allowed to eat or drink anything (except water), after 9 PM until study completion. At 5 AM, a primed ($25\text{ }\mu\text{C} \times \text{FPG}/100$)-continuous ($0\text{-}25\text{ }\mu\text{Ci}/\text{min}$) infusion of $[3\text{-}^3\text{H}]\text{glucose}$ (NEN, Boston, MA, USA) was started and continued until 12 noon. At 8 AM (time zero), subjects ingested 75 g of glucose containing $75\text{ }\mu\text{Ci}$ of $[1\text{-}^{14}\text{C}]\text{-glucose}$ (NEN). At 7 AM, blood samples for determination of plasma glucose and insulin concentrations and tritiated and ^{14}C -glucose radioactivity were drawn every 10–15 min until 12 noon. During the postabsorptive state, steady state conditions prevail and the basal rate of glucose appearance (R_a) equals the rate of total body glucose disappearance (R_d) and was determined as the ratio of the $[3\text{-}^3\text{H}]\text{-glucose}$ infusion rate (DPM/min) to the steady state plasma $[3\text{-}^3\text{H}]\text{-glucose}$ specific activity (DPM/mg). During the 30 min prior to ingestion of the glucose drink, all subjects achieved a steady state of plasma-tritiated glucose specific activity (change $<5\%$).

After glucose ingestion, total rates of glucose appearance (R_a) and glucose disappearance from the peripheral circulation (R_d) were computed from the $[3\text{-}^3\text{H}]\text{-glucose}$ data with the use of two-compartment model.^{18,19} Glucose clearance was calculated as the R_d divided by the plasma glucose concentration at each time point. The ^{14}C -glucose data are used to calculate the rate of appearance of oral glucose (R_{aO}) as follows. The plasma ^{14}C -glucose radioactivity was divided by the ^{14}C -glucose specific activity of the glucose drink to calculate the plasma ‘oral’ glucose concentrations that would be obtained in the systemic circulation if the sole source of glucose was from the oral load. These calculated ‘oral’

glucose concentrations and the [3-³H]-glucose data were then used to compute the rates of appearance of oral glucose in peripheral plasma (RaO), according to the same two-compartment model of the glucose system as employed to derive the total rate of glucose appearance. The rate of appearance of endogenous glucose (i.e. endogenous glucose production, EGP) was obtained as the difference between the total (³H-glucose) and oral (¹⁴C-glucose) rates of glucose appearance. All rates of glucose turnover were averaged over 15-min intervals. As 4 h is sufficient to allow complete absorption of the oral glucose load,^{14,20} the difference between the amount of glucose that was ingested and the amount of ingested glucose that appeared in the systemic circulation equals the amount of glucose that was taken up by the splanchnic (liver plus gut tissues) tissues.

Insulin sensitivity index (ISI) was calculated according to Matsuda *et al.*²¹ The basal hepatic insulin resistance index was calculated as the product of the fasting plasma insulin concentration and the basal rate of EGP. EGP is inhibited by insulin, and the relationship has been previously described.²² Over the range of plasma insulin concentrations that typically are seen under basal conditions (55 ± 3 to 75 ± 4 to 1110 ± 4 pmol/l), there is a linear relationship between the increase in plasma insulin concentration and the decrease in hepatic glucose production ($r = 0.92$, $P < 0.001$).²² An index of beta cell function was evaluated by calculating the ratio of the incremental insulin response (ΔI) to the incremental glucose response (ΔG) during the OGTT.¹⁶ Moreover, we calculated the insulinogenic index as the incremental rise in insulin to glucose during the first 30 min of the test ($\Delta I/\Delta G$ 30 min) which is an index of the first insulin release and the insulin secretion/insulin resistance ratio as the product of the incremental ratio of area under the curve of insulin to glucose for the first 2 h ($\Delta I/\Delta G$ 0–120 min) multiplied by rate of glucose disposal, which is similar to the disposition index.¹⁶

Analytical determinations

Plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma insulin concentration was measured by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA). Tritiated and ¹⁴Cglucose specific activities were determined on deproteinized barium/zinc plasma samples as previously described.^{12,13}

Statistical analysis

Data are given as the mean $\pm$ SEM. Statistical calculations were performed with StatView for Windows, version 5.0 (SAS Institute, Cary, NC). Differences between T2DM and NGT subjects were compared using the unpaired *t*-test when normally distributed and by Mann Whitney when showed a skewed distribution (such as insulin concentrations and all derived indexes using insulin). Values before and after pioglitazone treatment in T2DM were compared using the paired *t*-test when normally distributed and by Wilcoxon test when not normally distributed. Pearson correlation coefficient was calculated for univariate analysis. Variables with skewed distribution were log transformed before regression analysis. The relationship between glucose concentration at 2 h and mean glucose clearance during the first 2 h of OGTT can be described by a power function ($y = a \times x^{-b}$). Parameters a and b of equations were derived after log-log transformation of the data to give the function $\ln(y) = \ln(a) - b \times \ln(x)$. A *P* value of ≤ 0.05 was considered significant.

Results

Fasting parameters of study subjects

We studied 24 Mexican-American subjects, comprising 12 with T2DM and 12 with NGT who were matched for weight and BMI (Table 1). Diabetic subjects were in poor glycaemic

control with fasting plasma glucose concentration ($\text{FPG} = 10.5 \pm 0.7 \text{ mmol/l}$) and HbA1c ($9.7 \pm 0.7\%$) significantly higher than in NGT subjects (Fig. 1). Fasting plasma insulin (FPI) concentration tended to be increased in T2DM, indicating that insulin secretion was preserved, although beta cell function was deteriorated. Basal EGP (primarily reflects liver) in the two groups was not statistically different (Table 1). On the other hand, the hepatic insulin resistance index was approximately 17 times higher in T2DM, and the fasting glucose clearance was about half compared to NGT subjects. Thus, fasting hyperglycaemia was explained mainly by increased hepatic insulin resistance and reduced glucose clearance.

After 16 weeks of pioglitazone treatment, the FPG concentration in patients with T2DM decreased significantly (by $-2.7 \pm 0.5 \text{ mmol/l}$, $P = 0.0003$ vs baseline) and the HbA1c declined by $-2.2 \pm 0.6\%$, ($P = 0.003$) even though the FPI concentration decreased by 43% ($P < 0.01$). Fasting EGP decreased slightly and while hepatic insulin resistance declined by 49% ($P < 0.002$), despite an increase in body weight ($\Delta = 4.0 \pm 3.0 \text{ kg}$, $P = 0.003$).

Glucose metabolism during postabsorptive state

During the OGTT, the plasma glucose concentrations in patients with T2DM was two- to threefold greater than in NGT subjects at all time intervals ($P < 0.001$), despite higher plasma insulin concentrations ($P < 0.01$) (Fig. 1). During the initial 60 min following glucose ingestion, the excessive rise in plasma glucose concentration vs NGT was explained mainly by reduced glucose clearance (mean 0–60 min 1.3 ± 0.1 vs $3.1 \pm 0.3 \text{ ml/kg.min}$, $P < 0.0001$) and slightly by impaired suppression of EGP (mean 0–60 min 11.1 ± 1.5 vs $8.1 \pm 1.3 \text{ } \mu\text{mol/kg}_{\text{ffm}}.\text{min}$, $P = 0.10$). The ISI was also markedly reduced in T2DM subjects (2.14 ± 0.37 vs $25.64 \pm 2.56 \text{ (mmol/l} \times \text{pmol/l)}^{-1}$, $P < 0.0001$).

During the 4-h time period following glucose ingestion (Table 2), the Ra of oral glucose and suppression of EGP were similar in T2DM and NGT subjects but the glucose clearance rate remained markedly reduced. Thus, the initial (0–90 min) excessive rise in plasma glucose concentration could not be compensated by an increase in tissue glucose clearance, and the plasma concentration at 240 min remained markedly elevated in T2DM vs NGT subjects (12.2 ± 0.8 vs $4.6 \pm 0.2 \text{ mmol/l}$, $P < 0.001$) (Fig. 1). Although in T2DM the mean plasma insulin concentrations during the OGTT were significantly increased ($P < 0.01$ vs NGT), the index of insulin secretion normalized to insulin resistance (calculated as incremental ratio of insulin to glucose multiplied by glucose clearance) was markedly reduced (Table 2, $P < 0.05$), indicating a severe defect in beta cell function in response to the glucose load.

After 16 weeks of pioglitazone treatment, the mean plasma glucose concentration (0–240 min) during the OGTT was significantly reduced ($\Delta = -3.7 \pm 0.8 \text{ mmol/l}$, $P = 0.001$) in patients with T2DM without any change in the mean plasma insulin concentration (Table 1). Following pioglitazone, the total glucose Ra decreased significantly especially during the 0- to 120-min time period due mainly to a decrease in EGP (Table 2, Fig. 2).

We observed an increase in all parameters of beta cell function (Table 2) after 16 weeks of pioglitazone treatment, i.e. the insulinogenic index ($\Delta I/\Delta G$, 0–30 min) median values doubles ($P = 0.002$), the insulin secretion index ($\Delta I/\Delta G$) increased significantly during both the 0- to 120- ($P = 0.02$) and 0- to 240 ($P = 0.005$)-min time periods of the OGTT following pioglitazone, as well as the disposition index ($P < 0.01$).

Pioglitazone increased the ISI during the OGTT by 50% (from 2.14 ± 0.37 to 3.28 ± 0.42 , $(\text{mmol/l} \times \text{pmol/l})^{-1}$, $P < 0.002$) after pioglitazone (Table 2) but ISI remained significantly lower than in NGT subjects ($25.64 \pm 2.56 \text{ (mmol/l} \times \text{pmol/l)}^{-1}$, $P < 0.0001$). In agreement with that metabolic clearance rate (MCR) of glucose, which reflects the intrinsic ability of

tissues to take up glucose, was only slightly enhanced and remained significantly lower than in NGT subjects (Fig. 3).

Metabolic determinants of fasting and postprandial glycaemia and effect of pioglitazone treatment

In the total group of subjects (NGT and T2DM), fasting hyperglycaemia (FPG) was correlated with increased rate of EGP ($r = 0.50$, $P = 0.01$) and also with increased hepatic insulin resistance index ($r = 0.73$, $P = 0.0001$).

The decrease in FPG, observed after pioglitazone treatment, was associated with the decrease in hepatic insulin resistance index ($r = 0.57$, $P = 0.05$) and with the increase in fasting glucose clearance ($r = -0.64$, $P < 0.03$).

In the total group of subjects, we observed a hyperbolic relationship between the 2-h glucose clearance (MCR) and the 2-h plasma glucose concentration (measure of glucose tolerance) (Fig. 4). After log transformation of 2h-PG and MCR, data were fitted by linear regression ($r = 0.91$, $P < 0.0001$). Estimates of slope and intercept of the line were used to reconstruct the hyperbolic relationship as described in the method session. Although the changes in glucose clearance during OGTT were small after Pioglitazone treatment, the subjects moved along the curve towards the control subjects. To confirm this, we have found that the decrement in plasma glucose at 2-h correlated strongly with the increment in mean plasma glucose clearance during the first 2-h ($r = -0.74$, $P = 0.006$), with the increase in the insulin secretion index ($\Delta I/\Delta G$) ($r = -0.76$, $P = 0.004$) and the decrease in hepatic insulin resistance index ($r = 0.62$, $P = 0.006$).

Discussion

In this study, we explored the metabolic mechanisms via which the pioglitazone improves fasting and postprandial hyperglycaemia following glucose ingestion in Mexican-American subjects with type 2 diabetes and poor glycaemic control. For this purpose, we used a double tracer OGTT test that allows to measure during the same exam the rate of oral glucose absorption, the postprandial suppression of EGP, the metabolic glucose clearance rate (MCR) that is an index of peripheral insulin sensitivity, as well as indexes of beta cell function.

Consistent with previous results,^{8,11,18} pioglitazone decreased both the fasting and postprandial mean glucose concentration during the OGTT, even though FPI decreased and postprandial mean insulin concentration during the OGTT remained unchanged. Following 16 weeks of treatment, the basal EGP declined slightly, while the basal hepatic insulin resistance index decreased by 42%. The decrease in (fasting) hepatic insulin resistance was correlated with both the decrease in fasting as well as 2-h glucose concentration, demonstrating the important insulin-sensitizing effect of pioglitazone on the liver. We also evaluated the contribution of the splanchnic tissues (liver plus gastrointestinal) to the improvement in oral glucose tolerance following thiazolidinedione treatment. The rate of appearance of oral glucose into the systemic circulation was unchanged after pioglitazone treatment in agreement with a previous study from our group.¹⁸ Compared to that protocol, the patients that were studied here were more hyperglycaemic and had an increased glucose production, both during fasting as well as postprandial. Pioglitazone was effective in suppressing excessive endogenous (primarily hepatic) glucose production not only during fasting but also following glucose ingestion, despite no change in mean plasma insulin concentration during the OGTT (Fig. 2). We can speculate, based on the results of previous studies from our group,^{18,23} that this is mediated through a decrease in gluconeogenesis.

The effect of pioglitazone on glucose MCR, which reflects the intrinsic ability of tissues to take up glucose, was modest, and this study was underpowered to detect a significant improvement ($P = 0.07$). We found that although the MCR was slightly enhanced, it was far from returning close to values observed in control subjects (Figs 3 and 4). However, although small, the improvement in MCR was inversely associated with the decrease in mean and 2-h glucose concentration ($R = -0.74$, $P = 0.006$). This strong association was explained by the fact that 2-h glucose concentration was related to postprandial glucose clearance in a log-log fashion, i.e. by a hyperbolic function (Fig. 4). Thus, slightly higher postprandial glucose clearance in patients with T2DM can be associated with much lower 2-h glucose levels. This insulin-sensitizing effect on peripheral tissues was confirmed by the Matsuda ISI, which increased by 50%. This insulin-sensitizing effect of pioglitazone is consistent with previously published studies that have employed the insulin clamp technique to quantify insulin-mediated glucose disposal following thiazolidinedione treatment.^{7,9,11,18}

Insulin secretion was not impaired in this group of Mexican-Americans because the insulinogenic index and the ratio of incremental area of insulin to glucose were not different between T2DM and NGT subjects. However, T2DM were more insulin resistant, and when the insulin secretion was normalized for the insulin resistance, it resulted significantly lower than in NGT, showing impaired beta cell function. After 4 months of pioglitazone treatment, all indexes of insulin secretion and beta cell function improved and the index of insulin secretion normalized to insulin resistance became similar to the one observed in NGT subjects (from 996 ± 344 to 2560 ± 810 in T2DM vs 2382 ± 600 in NGT subjects).

In summary, the present results demonstrate that pioglitazone treatment for 4 months in Mexican-American subjects with poor blood glucose control improves glucose homeostasis during the OGTT mainly by improving beta cell function, enhancing hepatic insulin sensitivity and augmenting the suppression of endogenous (primarily hepatic) glucose production, while the effect on MCR of glucose was modest. These results emphasize the important effects (decreased basal and post-OGTT hepatic glucose production and improved beta cell function) of the thiazolidinediones on the liver during basal and post-OGTT states in patients with type 2 diabetes mellitus.

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Fig. 1. Plasma glucose and insulin concentrations during the oral glucose tolerance test (OGTT). Top panel: Glucose concentrations during the OGTT before (filled circle) and after pioglitazone treatment (open circle) compared to normal glucose tolerance subjects (dashed line). Bottom panel: Insulin concentrations during the OGTT.

Fig. 2.

TOP: The total rate of (exogenous plus endogenous) glucose appearance before and after pioglitazone therapy. The total Ra decreased significantly ($P < 0.02$) following 4 months of pioglitazone treatment. BOTTOM: Rates of oral glucose appearance (RaO) and endogenous glucose production before and after pioglitazone therapy.

Fig. 3.
The metabolic clearance rate (MCR) of glucose during the oral glucose tolerance test increased significantly ($P < 0.05$) following 4 months of pioglitazone treatment.

Fig. 4.

Relationship between mean metabolic clearance rate (MCR) of glucose during the oral glucose tolerance test (0–120 min) and glucose concentration at 120 min, in normal glucose tolerance (dark squares) and patients with T2DM before (open circles) and after (filled circles) 4 months of pioglitazone treatment. After a log-log transformation, data were fitted by linear regression ($r = 0.91$, $P < 0.0001$). Estimates of slope and intercept of the line were used to reconstruct the hyperbolic relationship as described in the method session.

Table 1

Clinical and metabolic parameters at baseline and after 16 weeks of pioglitazone

	Normal glucose tolerance (NGT)	T2DM _{Baseline}	T2DM _{treated}	P _{treatment}
Number	12	12	12	–
Age (years)	42 ± 4	54 ± 2	54 ± 2	–
Gender (M/F)	4/8	7/5	7/5	–
Weight (kg)	83.3 ± 3.3	81.9 ± 3.6	85.9 ± 3.9	0.003
BMI (kg/m ²)	30.4 ± 1.1	30.5 ± 1.1	32.0 ± 1.2	0.002
HbA1c (%)	5.7 ± 0.1	9.7 ± 0.7	7.5 ± 0.5	0.003
Fasting (mean – 300 min)				
Fasting plasma glucose (mmol/l)	5.4 ± 0.1	10.5 ± 0.7★	7.8 ± 0.6★	0.0003
Fasting plasma insulin (pmol/l)	28 ± 4	409 ± 70★	232 ± 35★	0.006
Endogenous glucose production (μmol/kg _{ffm} min)	18.1 ± 1.0	20.0 ± 1.1	17.3 ± 0.8	0.005
Basal hepatic IRI (μmol/kg _{ffm} min × pmol/ml)	492 ± 72	8194 ± 1513★	3989 ± 563★	0.002
Basal glucose clearance (ml/kg min)	2.03 ± 0.11	1.29 ± 0.05★	1.48 ± 0.10★	0.11

★ $P < 0.05$ vs NGT subjects.

Table 2

Metabolic parameters (0–120 and 0–240 min) during mixed meal at baseline and after 16 weeks of pioglitazone

	Normal glucose tolerance (NGT)	T2DM _{Baseline}	T2DM _{treated}	P _{treatment}
Oral glucose tolerance test (mean 0–240 min)				
Mean Glucose (mmol/l)	6.6 ± 0.2	16.1 ± 0.8★	12.4 ± 0.9★	0.001
Mean Insulin (pmol/l)	109 ± 12	610 ± 133★	696 ± 118★	0.94
EGP (μmol/kg _{ffm} min)	5.0 ± 0.8	6.4 ± 1.1	4.2 ± 0.6	0.04
Ra of oral glucose (μmol/kg _{ffm} min)	30.3 ± 2.9	32.4 ± 2.7	29.4 ± 2.1	0.17
Total Ra of glucose (μmol/kg _{ffm} min)	35.3 ± 2.3	38.9 ± 2.9	33.5 ± 1.9	0.02
Glucose Clearance (ml/kg min)	3.27 ± 0.19	1.52 ± 0.11★	1.81 ± 0.21★	0.07
Insulin sensitivity index (mmol/l pmol/l) ⁻¹	25.64 ± 2.56	2.14 ± 0.37★	3.28 ± 0.42★	0.002
Insulinogenic Index (ΔI/ΔG, 0–30 min) (pmol/mmol)	108 ± 32	105 ± 31	190 ± 49	0.002
Insulin Secretion Index (ΔI/ΔG, 0–120 min) (pmol/mmol)	74 ± 14	48 ± 17	107 ± 31★	0.01
Insulin Secretion Index ΔI/ΔG (0–240 min) (pmol/mmol)	61 ± 39	41 ± 17	118 ± 42	0.003
insulin secretion to insulin resistance ratio (0–120 min) (nmol/l) (mmol/l) ⁻¹ (μmol/min kg)	2382 ± 600	996 ± 344★	2560 ± 810	0.0096

EGP, endogenous glucose production; IRI, insulin resistance index.

★ $P < 0.05$ vs NGT.