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Thiazolidinediones increase hepatic insulin extraction in African Americans with impaired glucose tolerance and type 2 diabetes mellitus: A pilot study of rosiglitazone

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Abstract

Peripheral insulin levels are determined by beta-cell secretion, insulin sensitivity, and hepatic insulin extraction (HIE). We have previously shown that whereas sulfonylureas reduce insulin extraction, metformin enhances HIE. However, the effects of thiazolidinediones (TZDs) on HIE remain uncertain. Thus, we investigated the potential contribution of hepatic insulin clearance to peripheral insulin levels during rosiglitazone therapy in African Americans with impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DM). The study was composed of 12 first-degree relatives with IGT and 17 patients with newly diagnosed type 2 DM. Nineteen healthy relatives with normal glucose tolerance served as controls. Serum glucose, insulin, and C-peptide, and HIE (C-peptide–insulin molar ratios) were measured at $t = 0$ and 120 minutes during oral glucose tolerance test (OGTT) in all the subjects. The OGTT was performed before and after 3 months of rosiglitazone therapy (4 mg/d × 4 weeks and >8 mg/d × 8 weeks) in patients with IGT and type 2 DM. Insulin resistance index and beta-cell function were calculated in each subject using homeostasis model assessment (HOMA). Rosiglitazone therapy improved but did not normalize the overall glycemic control in the IGT and type 2 DM groups. After rosiglitazone therapy, the mean serum insulin and C-peptide levels at fasting remained unchanged. However, the 2-hour serum glucose and insulin were lower, whereas serum C-peptide was unchanged during 3 months of rosiglitazone treatment. Mean insulin resistance index of HOMA was reduced by 30% (4.12 ± 1.95 vs 6.33 ± 3.54, $P < .05$) in the type 2 DM group and by 21% (3.78 ± 2.45 vs 4.81 ± 3.49, P = NS) in the IGT group. Mean HIE values were significantly lower (70%) in the type 2 DM and IGT groups when compared with the normal glucose tolerance group. At 3 months, basal HIE was not significantly changed by rosiglitazone therapy in IGT and type 2 DM groups when compared with the baseline (0 month). However, rosiglitazone therapy was associated with increased HIE at 2 hours during OGTT by 40% and 30% in the IGT and type 2 DM groups, respectively, from the baseline (0 month) values. Furthermore, HIE inversely correlated with the insulin resistance index of HOMA ($r = -.46$, $P < .05$). We conclude that rosiglitazone therapy improved overall glucose tolerance and enhanced insulin sensitivity in patients with IGT and type 2 DM. Although basal HIE remained unchanged, rosiglitazone therapy increased postglucose challenge HIE in African Americans with IGT and type 2 DM. We speculate that TZDs increase insulin clearance or HIE after oral glucose challenge. This study suggests that in addition to insulin sensitization, rosiglitazone may be involved in insulin metabolism. The significance of the increased insulin clearance by TZD therapy remains uncertain and deserves further investigation in patients with insulin resistance and glucose intolerance.

1. Introduction

Peripheral insulin levels are determined by beta-cell secretion, insulin sensitivity, and hepatic insulin extraction (HIE). Recently, several new therapies have been introduced to reduce insulin resistance and/or improve insulin secretion in patients with type 2 diabetes mellitus (DM) [1-4]. We have previously shown that whereas sulfonylureas reduce insulin extraction [2], metformin enhances HIE in nondiabetic subjects [5]. However, the effects of thiazolidinediones (TZDs) on HIE remain uncertain [5,6]. In this regard, there has been increasing interest in the use of TZDs as backbone for managing insulin resistance in patients with impaired

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Table 1
Clinical and metabolic characteristics of African Americans with NGT, IGT, and type 2 DM before and after rosiglitazone therapy (3 months)

Parameter	NGT	IGT		Type 2 DM	
	Baseline	Baseline	Rosiglitazone	Baseline	Rosiglitazone
n	19	12		17	
Age (y)	49.1 ± 7.8	51.0 ± 9.3	–	49.0 ± 8.44	–
Body weight (kg)	86.8 ± 16.4	105.7 ± 27.8*	105.9 ± 28.7	102.7 ± 14.6*	101.8 ± 14.2
BMI (kg/m^2)	32.45 ± 6.69	40.16 ± 9.363*	38.8.45 ± 8.79.3	35.8 ± 4.4*	35.91 ± 3.88
Body fat mass (%)	42.2 ± 12.4	48.6 ± 12.8	49.2 ± 10.2	48. ± 5 12	49.42 ± 5.08
Blood pressure (mm Hg)					
Systolic	129 ± 14	139 ± 17.8	140 ± 17.5	136 ± 17	128 ± 15.9
Diastolic	77 ± 11.6	81.1 ± 8.50	76.4 ± 11.5	82 ± 11.7	75 ± 12

Values are expressed as mean ± SD.
* $P < .05$, IGT and type 2 DM vs NGT.

glucose tolerance (IGT) and type 2 DM [3,4,6,7]. Although TZDs improve insulin sensitivity as the primary mechanism(s) of action, this is often associated with a decreased or intact beta-cell secretion, as assessed by peripheral insulin levels. Indeed, in most previous studies, TZD therapy was often associated with reduction in peripheral serum insulin levels in the face of improved insulin sensitivity [3-7]. However, these studies did not examine the contributions of altered insulin clearance or HIE as an important mechanism for TZDs. We are aware of only one study by Kim et al [7] that showed that insulin clearance was increased in nondiabetic, insulin-resistant subjects during 3 months of rosiglitazone therapy. However, the effects of TZDs on insulin clearance in individuals with altered glucose tolerance such as those with impaired glucose tolerance and type 2 DM who are often prescribed the drugs were not studied.

Because African Americans and other high-risk populations with insulin resistance have decreased HIE [8-17] as a major contributor to the peripheral hyperinsulinemia in nondiabetic subjects, we sought to (1) examine HIE in African Americans with varying degrees of glucose tolerance and (2) to answer the question as to whether improvement of insulin resistance leads to changes in insulin clearance. To this end, we investigated the effects of a potent TZD (Rosiglitazone, GlaxoSmithKline Pharmaceutical, Philadelphia, PA) on glucose homeostasis, insulin action, and insulin secretion as well as HIE in African Americans with IGT and type 2 DM.

2. Subjects, materials, and methods

2.1. Populations

We studied 48 African Americans with varying degrees of glucose tolerance. There were 12 patients with IGT and 17 newly diagnosed, drug-naive patients with type 2 DM. Nineteen subjects with normal glucose tolerance (NGT) served as healthy controls. Informed written consent approved by the institutional review board for human biomedical research at the Ohio State University, Columbus, was obtained from each subject after the risks entailed in the study have been thoroughly explained.

All the subjects visited the Endocrine Research Unit of the Division of Endocrinology, Diabetes and Metabolism, The Ohio State University, Columbus, after a 10- to 12-hour fasting. After at least 10 minutes bed rest, 2 blood pressure readings were taken using zero-centered sphygmomanometer at 10-minute intervals. Each subject was weighed to the nearest gram and the height was measured to the nearest centimeter. Body composition was measured using dual-energy x-ray absorptiometer (Lunar, Madison, WI). The subjects who qualified for the study then underwent a standard oral glucose tolerance test (OGTT). The clinical characteristics of our African Americans with varying degrees of glucose tolerance are shown in Table 1. We excluded patients with symptoms of hyperglycemia such as polyuria, polydipsia, polyphagia, excessive thirst, recent weight loss, blurred vision, and so on, during screening. The following subjects were also excluded: (*a*) those taking medications known to influence glucose and insulin metabolism; (*b*) those individuals with liver, heart, lung, and kidney diseases; (*c*) those with established diabetes on antidiabetic medications; (*d*) those who participated in endurance exercise or indulged in regular competitive sport; and (*e*) those who have participated in weight reduction program during the last 6 months.

2.2. Metabolic studies

All the subjects were admitted to the Endocrine/Diabetes Clinical Research Unit of the Ohio State University, Columbus, after 10- to 12-hour overnight fasting. With the subject in the sitting position, an intravenous needle was inserted into a forearm vein. Blood samples were drawn for serum glucose, insulin, and C-peptide levels, and hemoglobin A_{1c} (HbA_{1c}) levels as well as routine kidney and liver function and hematologic tests in all subjects.

2.3. Oral glucose tolerance test

The subjects ingested 75 g (250 mL) of oral glucose load (Glucola, Baltimore, MD) over a 2-minute period. Blood

Table 2
Metabolic characteristics of African Americans with NGT, IGT, and type 2 DM before and after rosiglitazone therapy (3 months)

Parameter	NGT	IGT		Type 2 DM	
	Baseline	Baseline	Rosiglitazone	Baseline	Rosiglitazone
Metabolic parameters					
Fasting glucose (mg/dL)	85.2 ± 12.2	111.7 ± 13.5	100.1 ± 18.3	164.0 ± 71.76	127.1 ± 51.6‡
2-h PP glucose (mg/dL)	85.6 ± 20.1	162.1 ± 22.5	122.1 ± 41.2	289.2 ± 102.3	199.6 ± 105.0‡
Fasting insulin (μU/mL)	13.01 ± 9.32	15.40 ± 9.16	17.32 ± 9.39	14.91 ± 8.43	13.71 ± 5.04
2-h PP insulin (μU/mL)	72.75 ± 87.7	69.5 ± 43.7	72.50 ± 49.36	89.72 ± 50.18	71.9 ± 54.4‡
Fasting C-peptide (ng/mL)	3.68 ± 1.44	3.61 ± 1.34	3.79 ± 1.42	4.88 ± 2.26	3.88 ± 1.23
2-h C-peptide (ng/mL)	10.10 ± 4.12	11.31 ± 2.31	11.72 ± 3.66	9.48 ± 3.53	10.66 ± 4.32
HbA_{1c} (%)	5.7 ± 0.5	6.06 ± 0.53	5.60 ± 0.39	7.77 ± 2.10	6.96 ± 2.01
HOMA -IR	2.81 ± 2.01	4.81 ± 3.49‡	3.78 ± 2.45	6.33 ± 3.54‡	4.12 ± 1.95‡
HOMA-%B	252 ± 187	132 ± 62	191.2 ± 169	110.6 ± 84	106.9 ± 61.6
HIE					
0 min	17.12 ± 16.34*	10.85 ± 3.07	12.95 ± 5.42	12.99 ± 4.41	13.83 ± 4.70
2 h	8.44 ± 3.35	5.72 ± 3.10	8.88 ± 3.28**	7.24 ± 8.23	10.08 ± 8.12

Values are expressed as mean ± SD. PP = postprandial.
[a] $P < .01$ vs controls.
* $P < .01$, 3 months vs baseline.
** $P < .02$, 3 months vs 0 month (IGT).
‡$P < .001$, IGT and type 2 DM vs NGT (IGT).

samples were obtained at $t = 0$ minute and 2 hours after oral glucose load for serum glucose, insulin, and C-peptide levels. The categories of glucose tolerance were defined according to Expert Committee on the Diagnosis of Diabetes [18].

2.4. Longitudinal study

The patients with IGT and type 2 DM received rosiglitazone (4 mg/d) orally daily for the initial 4 weeks each morning before breakfast. The dose was then increased to 8 mg/d in the morning from 4 to 12 weeks. The subjects were seen at the outpatient clinical research unit at 4 weekly intervals after a 10- to 12-hour overnight fasting. History and physical examination were performed at each visit. Fasting blood was drawn for fasting glucose, liver, and renal function tests, and HbA_{1c} levels at baseline (0 month) and after 3 months of rosiglitazone therapy. The OGTT was repeated at 3 months of rosiglitazone treatment.

2.5. Analytical methods

Serum glucose concentrations were measured by the glucose oxidase method using glucose autoanalyzer (Yellow Spring Instruments, Yellow Spring, OH). The serum insulin and C-peptide levels were determined by a standard double-antibody radioimmunoassay technique at the core laboratories of the Ohio State University hospitals, Columbus. The sensitivity of the insulin assay was 2.5 μU/mL. The intra- and interassay coefficients of variation were 6% and 10%, respectively. The lower limit of the C-peptide assay was 0.47 ng/mL and the intra- and interassay coefficients of variation were 7% and 13%, respectively. The HbA_{1c} level was measured by the immuno-based method (DCA 2000, Bayer, Indianapolis, IN). The reference range was 3.6% to 6.1%.

2.6. Calculations and statistical analyses

The body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Hepatic insulin extraction was calculated as the molar ratios of C-peptide and insulin levels at fasting and 2 hours during the OGTT as previously described [9,17,19]. We designated HIE to reflect insulin clearance based on the known kinetics of both insulin and C-peptide levels and the limitations in nonsteady state [16-22]. The noninvasive method to calculate hepatic insulin extraction was based on the following assumptions: (1) that portal insulin and C-peptide are present in 1:1 equimolar proportions; (2) although insulin is extracted by the liver, C-peptide is not; and (3) that C-peptide kinetics are not altered in the physiologic concentrations in the healthy subjects with normal renal function [19]. The insulin resistance and beta-cell function were calculated using homeostasis model assessment (HOMA). Insulin resistance index was calculated using the homeostasis model assessment (HOMA-IR) as follows: fasting insulin (μU/mL) × fasting plasma glucose (mmol/mL)/22.5. Homeostasis model assessment–derived beta-cell function (HOMA-%B) was also calculated by the formula: 20 × fasting insulin (μU/mL)/fasting glucose (mmol/mL) − 3.5.

Results are expressed as mean ± SD, unless stated otherwise. Statistical analyses were performed using Student t test (paired) within the group analyses and unpaired t test between the group analyses and analysis of variance with repeated measures, where appropriate. Bonferroni method was used for post hoc testing. The nonparametric data were analyzed using χ^2 test. The relationships of HIE with HOMA-IR and HOMA-%B were calculated using least square method as well as stepwise linear regression. For comparison of the mean data with unequal variance,

Newman-Keuls multiple *t* test was used. *P* value of less than .05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of subjects

The mean body weight and BMI were significantly ($P < .05$) higher in the IGT and type 2 DM groups than in the NGT group. Surprisingly, during rosiglitazone therapy, the mean body weight and BMI were not significantly changed in the IGT and type 2 DM groups. Rosiglitazone treatment was well tolerated without clinical evidence of pitting edema or congestive heart failure. Rosiglitazone had no adverse effects on liver function or hematologic parameters in the IGT and type 2 DM groups (Table 1).

3.2. Effects of rosiglitazone on glucose homeostasis, insulin secretion, and insulin resistance in African Americans with IGT and type 2 DM

As shown in Table 2, the IGT and type 2 DM groups were significantly more insulin-resistant and had decreased beta-cell function when compared with the NGT group at baseline. Fasting serum glucose did not change in the IGT group during the rosiglitazone treatment when compared with the baseline (0 month). However, the 2-hour serum glucose levels during OGTT were significantly decreased during rosiglitazone treatment in the IGT group. Both fasting and 2-hour serum glucose levels during OGTT were significantly decreased during rosiglitazone treatment in the type 2 DM group (Table 2). Furthermore, HbA_{1c} slightly but significantly decreased in the IGT and type 2 DM groups during rosiglitazone therapy.

As shown in Table 2, mean fasting serum insulin levels were not different in the IGT and type 2 DM groups when compared with the NGT group. However, mean 2-hour serum insulin levels were significantly lower in the IGT and type 2 DM groups than in the NGT group. The mean 2-hour serum insulin levels during OGTT were slightly lower, but not significantly changed from baseline (0 month), during rosiglitazone therapy in the IGT and type 2 DM groups. The serum C-peptide levels did not change during rosiglitazone treatment in both the IGT and type 2 DM groups (Table 2). As shown in Table 2, rosiglitazone treatment decreased slightly, but insignificantly, the HOMA-IR in the IGT when compared with the baseline (0 month) value (P = NS). In contrast, in the type 2 DM group, rosiglitazone significantly decreased the HOMA-1R when compared with the baseline (0 month) (Table 2).

3.3. Hepatic insulin extraction during OGTT

The mean HIE was significantly ($P < .01$) lower in the IGT and type 2 DM groups when compared with the NGT group. After rosiglitazone therapy, mean basal HIE did not change in the IGT and type 2 DM groups. However, we found that 2-hour postprandial HIE increased by 30% and 40% in the IGT and type 2 DM groups after rosiglitazone therapy, respectively. We found that HIE correlated with HOMA-IR ($r = -0.46$, $P < .05$) and HOMA-%B ($r = -0.498$, $P = .042$) (Table 2).

4. Discussion

Insulin resistance is often associated with compensatory hyperinsulinemia to maintain normal glucose tolerance test in nondiabetic subjects. Typically, in healthy subjects, the hyperinsulinemia originates basically from 2 sources, that is, by beta-cell hypersecretion and/or decreased insulin clearance predominantly in the liver. Thus, HIE plays a critical role in determining the peripheral insulin levels in humans. Indeed, we [11,12,17-22] and others [12,21] have demonstrated that hyperinsulinemia and concomitant insulin resistance and decreased HIE coexist in nondiabetic African American adults and children. We have recently shown that different oral antidiabetic medications, for example, sulfonylureas and biguanides, have varying effects on insulin secretion and HIE (insulin clearance) [2,5,7]. Therefore, we extended our studies to address the question as to whether TZDs also change HIE in our African Americans with IGT and type 2 DM.

Thiazolidinediones are known to improve insulin resistance and overall glucose control in patients with type 2 DM [1-4]. Typically, the improvement in insulin sensitivity during TZDs is often associated with reduced serum insulin levels despite weight gain [1-4]. However, the mechanism of the reduced circulating insulin levels remains uncertain, but has been partly attributed to reduced demand on beta-cell secretion (due to improvement in peripheral insulin resistance). As expected, in the present study, rosiglitazone monotherapy improved the overall glycemic control as assessed by fasting and 2-hour postprandial glucose and HbA_{1c} in the IGT and type 2 DM groups. The mean insulin resistance index (HOMA-IR) was significantly higher in the IGT and type 2 DM groups than in the NGT group. Rosiglitazone decreased the HOMA-IR in both the African Americans with IGT and type 2 DM. However, mean fasting insulin and C-peptide were however not significantly changed by rosiglitazone therapy in the African American patients with IGT and type 2 DM. When we compared beta-cell secretion by serum C-peptide levels, we found some dissociation between serum C-peptide and corresponding circulating insulin levels at 2 hours during oral glucose challenge in the patients with IGT and type 2 DM treated with rosiglitazone. Insulin levels were lower, whereas the corresponding C-peptide did not change, suggesting increased insulin clearance. This was confirmed by the 2-hour hepatic insulin extraction values in both glucose-intolerant groups. Our findings suggested that the preexisting lower HIE in our patients was significantly improved by rosiglitazone therapy in our African Americans with IGT and type 2 DM.

Oral antidiabetic medications with different mechanisms of actions improve glucose control in patients with IGT and type 2 DM. However, the impact of oral antidiabetic drugs in

insulin metabolism has not been adequately addressed in the past. We were therefore extremely interested in the role of TZDs on insulin clearance as a potential mechanism of reduced circulating serum insulin in our patients with glucose intolerance. In this regard, we are aware of only one study by Kim et al [7] who reported that rosiglitazone therapy increased both exogenous and endogenous insulin clearance in nondiabetic, but insulin-resistant overweight subjects. We have previously reported that Glucotrol XL, a potent beta-cell secretagogue, reduced hepatic insulin extraction and significantly contributed to the peripheral insulin levels in nondiabetic African Americans [2]. In contrast, we have also shown that Metformin, an insulin sensitizer, enhanced hepatic insulin extraction in nondiabetic African Americans [5,6]. In the present study, we found that basal HIE or insulin clearance was significantly lower in patients with IGT and type 2 DM when compared with the NGT group. Most importantly, although 3 months of rosiglitazone therapy had no significant effect on the basal HIE, it significantly increased HIE at 2-hour values during the OGTT in African Americans with IGT and type 2 DM. Our findings extend the recent observation by Kim et al [7] that showed that rosiglitazone therapy improved insulin clearance during steady-state glucose infusion test to oral glucose ingestion. We should note that increased HIE has also been observed in patients who undergo successful weight reduction by lifestyle modification [21] and biliopancreatic duct surgery [22]. Taken together, our current and previous studies lend credence to the idea that improvement in peripheral insulin resistance might result in concomitant increases in HIE by as yet ill-defined mechanism. Because our study was not a placebo-controlled, randomized, double-blind study, we suggest that such a study will be necessary to confirm the current findings. Finally, we studied only African Americans. Thus, caution should be exercised in extrapolating our findings to other ethnic and racial groups.

In summary, rosiglitazone therapy was effective in improving overall, long-term glucose control and reduced insulin resistance in our African Americans with IGT and type 2 DM. Our present study demonstrated that HIE or insulin clearance was significantly lower in African American subjects with IGT and type 2 DM when compared to those with NGT. Rosiglitazone therapy increased HIE after oral glucose challenge in the IGT and type 2 DM groups. We conclude that an increased HIE should be considered as one of the putative, pharmacologic actions of TZDs in patients with insulin resistance, IGT, and type 2 DM in high-risk African Americans. Whether other TZD subclasses with predominantly γ, α, or δ properties also increase in vivo hepatic insulin extraction or insulin clearance in humans remain to be investigated.

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