The Effect of Rosiglitazone on Urine Albumin Excretion in Patients With Type 2 Diabetes Mellitus and Hypertension

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Background: Thiazolidinediones are antidiabetic agents that improve insulin sensitivity (IS). Accumulating data indicate that these agents provide beneficial effects beyond glycemic control, such as improvement in vascular function. The aim of this study was to determine the effect of rosiglitazone on urine albumin excretion (UAE) in patients with type 2 diabetes mellitus (DM) and hypertension.

Methods: The study involved 20 subjects with type 2 DM who were already on 15 mg glibenclamide daily but were achieving poor glycemic control and who had either poorly controlled or newly diagnosed hypertension. In these patients, rosiglitazone (4 mg daily) was added to the existing therapeutic regimen for 26 weeks. At baseline and the end of the treatment, subjects gave a 24-h urine collection for direct measurement of albumin and a spot specimen for determination of the albumin-to-creatinine ratio (ACR). Subjects also had a hyperinsulinemic euglycemic clamp and an ambulatory blood pressure (BP) monitoring.

Results: At the end of the study, UAE was significantly reduced versus baseline, as measured either directly in the 24-h collection (22.4 ± 4.6 *v* 13.8 ± 3.0 mg/day, $P < .05$) or with ACR (20.9 ± 3.8 *v* 14.0 ± 2.8 mg/g, $P < .05$). The percentage changes in UAE (ΔALB for the 24-h collection and ΔACR for ACR) correlated with the respective changes in IS ($r = -0.64$, $P < .01$ for ΔALB and $r = -0.48$, $P < .05$ for ΔACR), systolic BP ($r = 0.63$, $P < .01$ and $r = 0.58$, $P < .01$ respectively), and diastolic BP ($r = 0.56$, $P < .05$ and $r = 0.50$, $P < .05$ respectively).

Conclusions: In this study, treatment of type 2 diabetic hypertensive patients with rosiglitazone significantly decreased UAE. Lowering of BP and improvement of IS should play roles in this UAE reduction. Am J Hypertens 2005;18:227–234 © 2005 American Journal of Hypertension, Ltd.

Key Words: Rosiglitazone, urinary albumin excretion, electrolytes, type 2 diabetes mellitus, hypertension.

The metabolic syndrome is a cluster of disorders that represent risk factors for cardiovascular disease (CVD), such as insulin resistance (IR), type 2 diabetes mellitus (DM), hypertension, abdominal obesity, and dyslipidemia.[1] Since the initial descriptions of the syndrome, IR was proposed to be the primary disorder and all of the other disturbances secondary to it.[2] In addition to those basic components, many other disturbances have been proposed to be members of the syndrome, such as hyperuricemia, elevated plasminogen activator inhibitor (PAI)–1, and others. Among the latter, microalbuminuria seems the most important and has been included in the criteria for the syndrome as defined by the World Health Organization.[1]

Microalbuminuria is defined quantitively as urine albumin excretion (UAE) of 30 to 300 mg/day, 20 to 200 μg/min in timed urinary collection, or 30 to 300 mg albumin/g creatinine in a spot specimen.[3,4] It is considered to be an indicator of vascular injury and the first sign of renal involvement in diabetic patients.[5,6] Diabetic patients with microalbuminuria are considered as having incipient nephropathy, whereas their progression to macroalbuminuria is a sign of clinical or overt

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nephropathy.[3,4] The prevalence and the severity of microalbuminuria increase with the duration and the severity of type 2 DM and hypertension.[7] The great majority of individuals with type 2 DM with microalbuminuria are also hypertensive; thus, from a practical point of view, the patient with type 2 DM, nephropathy, and hypertension represents a unified problem.[6] Apart from predicting diabetic renal disease progression, microalbuminuria is a prognostic marker of CVD and mortality in both diabetic and nondiabetic individuals[7–9]; therefore, its presence is a sign for aggressive intervention to reduce all cardiovascular risk factors.[4]

Thiazolidinediones (TZD) constitute a new class of agents for the treatment of type 2 DM that improve insulin action and thus reduce hyperglycemia. The TZD decrease IR through activation of the peroxisome proliferator–activated receptor gamma, which is involved in the regulation of genes controlling glucose and lipid metabolism.[10,11] Accumulating data indicate that TZD possess vasculoprotective properties, such as control of vascular cell proliferation and migration after injury, decrease of the plasma in C-reactive protein levels and PAI-1 activity, decrease of the intima-media thickness of the carotid arteries, restoration of blunted endothelium-mediated vasodilation in insulin-resistant states, and others.[10,11]

With regard to microalbuminuria, before this study was designed there were published data indicating a favorable effect of TZD from studies in animal models[12] and in patients with type 2 DM and microalbuminuria, but mostly not hypertension, without parallel reliable measurements of IR or blood pressure (BP).[13,14] Therefore, the primary aim of this study was to determine the effect of the TZD rosiglitazone on urine albumin excretion in relation to IR and BP changes in patients with type 2 DM and hypertension. In addition, this study aimed to evaluate the effect of rosiglitazone on renal function and serum electrolytes.

Methods

Study Population

The present study was conducted in the same diabetic hypertensive patients and with the same protocol as a study aiming to evaluate the effects of rosiglitazone on BP, which have been published elsewhere.[15] At baseline, 24 subjects (12 men and 12 women) were evaluated. All had type 2 DM and were already on treatment with 15 mg of glibenclamide daily but with poor glycemic control. Among them, 12 had a previous diagnosis of essential hypertension and were receiving antihypertensive treatment but were not having their BP controlled. The rest had newly detected hypertension and were not taking antihypertensive medication. The patients volunteered for the study after receiving information about it. Two of them subsequently refused to undergo the second clamp test and one could not undergo it because of difficulties in intravenous access. One subject refused the second ambulatory blood pressure monitoring (ABPM). Therefore, the final study group included 20 subjects with complete data sets. The study was approved by the review board of the Division of Medicine of Aristotle University of Thessaloniki, and participants provided informed consent before enrollment.

Study Protocol

To establish either the inadequate control of a previously diagnosed hypertension, or the recent diagnosis of mild hypertension, subjects were initially evaluated at the Hypertension Outpatient Clinic at three separate visits with use of the threshold of 140/90 mm Hg. On the initial visit participants had a screening physical examination and laboratory tests to exclude subjects with congestive heart failure, coronary artery disease, renal failure, liver disease, or history of malignancy.

Participants were admitted to our clinical research laboratory where at 07:00 (day 1) without morning medication and after 12-h fast blood samples were drawn for fasting plasma glucose and insulin, glycosylated hemoglobin (HbA_{1c}), renal function tests, serum electrolytes and routine laboratory parameters. On this day subjects had the 24-h urine collection and the ABPM, as described below. On the next morning (day 2), subjects came back to the laboratory to have their insulin sensitivity determined with the clamp technique. On day 3, subjects gave a random first-voided urine specimen to determine the albumin-to-creatinine ratio (ACR).

After these tests, rosiglitazone (4 mg once daily) was added. Absolutely no change was made in the pre-existing sulphonylurea or antihypertensive treatment throughout the study. Subjects were strictly advised to keep their physical activity and dietary habits unchanged during treatment. All subjects were evaluated every 2 months with a physical examination and routine laboratory tests. After 26 weeks of treatment they again underwent all of the previously mentioned tests. To avoid any seasonal variation in BP that could influence the results, all subjects were evaluated within a 2-month period in the spring and autumn.

Urinary Albumin Excretion Measurements

Urinary albumin was measured in two ways. The first was the direct measurement of albumin in a 24-h urine collection performed on day 1 with a nefelometric method using the Behring Nefelometer 100 (Dade Behring Inc., Deerfield, IL). In addition, ACR was measured in a random, first morning-voided urine specimen with a DCA 2000 Analyzer (Bayer Corp., Elkhart, IN), in which albumin was measured with an immunoturbidometric method.

Insulin Sensitivity Measurements

Insulin sensitivity (IS) was estimated using the hyperinsulinemic euglycemic clamp technique, as described elsewhere.[16,17] Briefly, two intravenous lines were placed, one into a hand or wrist vein by retrograde cannulation for blood sampling and the other into an antecubital vein for