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The effect of rosiglitazone on novel atherosclerotic risk factors in patients with type 2 diabetes mellitus and hypertension
An open-label observational study

Panteleimon A. Sarafidis[a,*], Anastasios N. Lasaridis[a], Peter M. Nilsson[b], Tzant F. Mouslech[a], Areti D. Hitoglou-Makedou[c], Panagiotis C. Stafylas[a], Kiriakos A. Kazakos[a], John G. Yovos[a], Achilleas A. Tourkantonis[a]

[a]*1st Department of Medicine, AHEPA University Hospital, Aristotle University, 54636 Thessaloniki, Greece*
[b]*Department of Medicine, Malmö University Hospital, Lund University, SE-205 02 Malmö, Sweden*
[c]*Biochemical Laboratory, 2nd Department of Pediatrics, AHEPA University Hospital, Aristotle University, 54636 Thessaloniki, Greece*

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Abstract

Thiazolidinediones are antidiabetic agents that decrease insulin resistance. Emerging evidence indicates that they present beneficial effects for the vasculature beyond glycemic control. The aim of this open-label observational study was to determine the effect of the thiazolidinedione rosiglitazone on novel cardiovascular risk factors, namely, lipoprotein(a) [Lp(a)], C-reactive protein (CRP), homocysteine, and fibrinogen in patients with type 2 diabetes and hypertension. A total of 40 type 2 diabetic patients already on treatment with 15 mg of glibenclamide daily and with poorly controlled or newly diagnosed hypertension were included in the study. Twenty of them received 4 mg of rosiglitazone daily as added-on therapy, whereas the rest remained on the preexisting antidiabetic treatment for 26 weeks. At baseline and the end of the study, subjects gave blood tests for the determination of Lp(a), CRP, homocysteine, fibrinogen, serum lipids, apolipoprotein (apo) A-I, and apo B. At the end of the study, rosiglitazone treatment was associated with significant reductions in Lp(a) (10.5 [8.9-54.1] to 9.8 [8.0-42.0] mg/dL, $P < .05$) and CRP levels (0.33 [0.07-2.05] to 0.25 [0.05-1.84] mg/dL, $P < .05$) vs baseline. Homocysteine levels were not affected but plasma fibrinogen presented a significant increase (303.5 ± 75.1 to 387.5 ± 70.4 mg/dL, $P < .01$) with rosiglitazone. Although no significant changes were observed in the rosiglitazone group for triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein (LDL) cholesterol, both apo A-I and apo B presented small significant reductions and the LDL–apo B ratio was significantly increased. None of the above parameters were changed in the control group. In conclusion, rosiglitazone treatment had a beneficial impact on Lp(a), CRP, and LDL particles' lipid content in type 2 diabetic hypertensive patients but not on homocysteine and fibrinogen. The overall effect of rosiglitazone on cardiovascular risk factors seems positive but must be further evaluated.

1. Introduction

Diabetes mellitus (DM) is one of the major risk factors for cardiovascular disease (CVD), and atherosclerotic complications are by far the most important cause of death in diabetic patients [1,2]. The cardiovascular risk of patients with type 2 DM is more elevated because of the coexistence of other traditional CVD risk factors, such as hypertension, elevated plasma triglycerides, low high-density lipoprotein cholesterol (HDL-C), and visceral adiposity within the metabolic syndrome [3,4]. In fact, this clustering seems to add substantial cardiovascular risk above and beyond the individual risk factors [5,6]. Insulin resistance (IR), the primary disorder of the syndrome, and compensatory hyperinsulinemia are believed to be associated with a higher risk of CVD, independently of the other components of the syndrome [7,8], and this may explain part of the additional risk. Moreover, a number of novel cardiovascular risk factors, which seem to contribute to the complex event of atherosclerosis, or at least reflect the activity of atherosclerotic processes, such as plasminogen activator inhibitor-1, C-reactive protein (CRP), and small-dense low-density lipo-

* Corresponding author. Tel.: +30 2310 994616; fax: +30 2310 994615.
E-mail address: psarafidis11@yahoo.gr (P.A. Sarafidis).

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protein (LDL) particles, may also be a part of the syndrome [9-11] and thus contribute to the excess CVD risk of it.

Thiazolidinediones (TZDs) are a newer class of antihyperglycemic agents that improve insulin action in skeletal muscles, liver, and adipose tissue through activation of the peroxisome proliferator–activated receptor γ [12,13]. By reducing IR and lowering the requirements in insulin, these compounds improve glycemic control in type 2 diabetic patients [12,13]; thus, they are currently used as antidiabetic drugs. Until the design of this study, emerging evidence suggested that TZDs presented beneficial effects on CVD risk factors beyond glycemic control, such as blood pressure, triglycerides, HDL-C, small-dense LDL particles, plasminogen activator inhibitor–1, and others [12-17]. Therefore, the primary aim of this study was to determine whether add-on treatment with rosiglitazone, one of the newer TZDs, in patients with both type 2 DM and hypertension would have a positive effect on some novel cardiovascular risk factors, that is, lipoprotein(a) [Lp(a)], CRP, homocysteine, and fibrinogen. Another purpose was to evaluate the effect of rosiglitazone on the levels of apolipoprotein (apo) A-I and apo B to detect possible changes in LDL particles' content.

2. Subjects and methods

2.1. Patients

A total of 40 subjects (18 men and 22 women) were included in the study. All subjects had type 2 DM, already on treatment with a sulfonylurea (15 mg of glibenclamide daily). Half of them had a previous diagnosis of hypertension and were on antihypertensive treatment but were not having their BP controlled. The rest had a newly detected hypertension and were not receiving antihypertensive medication. None of the subjects were receiving hypolipidemic medication. Twenty of the subjects (9 men and 11 women) were assigned after the baseline evaluation to 4 mg of rosiglitazone daily for 26 weeks (rosiglitazone group). The remaining 20 subjects (matched for age, sex, weight, duration of DM, previous or recent diagnosis of hypertension, and type of antihypertensive treatment) went on only with glibenclamide for the same period to serve as matched controls (control group). All the examinations were conducted in accordance with the Declaration of Helsinki (1989 amendment). The study was approved by the Division of Medicine, Faculty of Medicine, Aristotle University of Thessaloniki, and participants provided informed consent before the enrollment. It has to be noted that patients from the rosiglitazone group served also as the population of another study of our group aiming to evaluate the effects of rosiglitazone on blood pressure, which have been previously published [18].

2.2. Study protocol

Patients had initially a screening physical examination and laboratory tests and if they had congestive heart failure, coronary artery disease, renal failure, anemia, liver disease or history of malignancy, drug or alcohol abuse they were excluded from the study. Study participants were admitted to the clinical research laboratory of our department where at 07:00 AM, after 12-hour fast and without morning medication, blood samples were drawn to determine the levels of fasting plasma glucose and insulin, glycated hemoglobin (hemoglobin [Hb] A_{1c}), total cholesterol, triglycerides, HDL-C and LDL cholesterol (LDL-C), apo A-I, apo B, Lp(a), high-sensitive CRP (hs-CRP), homocysteine, fibrinogen, and routine laboratory parameters. From fasting plasma glucose and insulin values, the IR of the subjects was determined with the use of the homeostasis model assessment (HOMA) index, according to the model: HOMA-IR = [fasting glucose (mmol/L) × fasting insulin (μU/mL)]/22.5, as described previously [19]. Subjects also had their body weight and height measured and their body mass index (BMI) calculated. In addition, in every patient the minimal circumference at the height of the navel and the widest circumference at the height of the hips were measured to estimate waist-to-hip circumference ratio (WHR) [20]. Finally, all subjects had their body composition analyzed by bioelectrical impedance analysis [21] with the use of the Bodystat1500 device (Bodystat Ltd, Douglas, Isle of Man, British Isles).

After completing all tests, rosiglitazone 4 mg once daily (every noon) was added in the first group of subjects, whereas the second group went on with the underlying treatment. The glibenclamide treatment and the antihypertensive medications (if any) remained completely unchanged throughout the study. Subjects were strictly advised to keep their physical activity and diet habits also unchanged. Subjects visited the outpatient clinic every 2 months for a physical examination and routine laboratory tests. After 26 weeks they were again admitted to the research laboratory for all the above tests.

2.3. Analytical methods

Plasma glucose, triglycerides, total cholesterol, HDL-C and LDL-C, and routine biochemical parameters were measured with Roche/Hitachi 912 automatic analyzer (Roche Diagnostics, Basel, Switzerland) using standard laboratory methods. Hemoglobin A_{1c} was measured with high-performance liquid chromatography (Menarini Diagnostics, Florence, Italy) with a normal reference range of 4.2% to 6.2%. Plasma insulin concentration was determined by radioimmunoassay (DiaSorin, Saluggia, Italy). Total plasma apo A-I, apo B, and Lp(a) were determined by immunonephelometry, using the Behring Nefelometer 100 (Dade Behring Inc, Deerfield, Ill). Homocysteine was measured with fluorescence polarization immunoassay, using Abbot IMx analyzer (Abbot Diagnostics, Abbot Park, Ill). Plasma fibrinogen concentration was also determined by a commercial nephelometric assay (Dade Behring Inc) and hs-CRP was measured using a latex-enhanced immunonephelometric method (Dade Behring Inc).