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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

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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-

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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).

Table 1
Background characteristics of the subjects

	Rosiglitazone group	Control group
n	20	20
Men/women	9/11	9/11
Previous/recent diagnosis of hypertension	10/10	10/10
Age (y)[a]	63.8 ± 6.4	61.7 ± 7.0
Duration of DM (y)[a]	9.8 ± 6.4	9.1 ± 7.2
Weight (kg)[a]	74.7 ± 9.1	75.6 ± 8.1
BMI (kg/m^2)[a]	27.4 ± 2.9	27.6 ± 3.8
WHR[a]	0.93 ± 0.07	0.95 ± 0.06
Fasting glucose (mg/dL)[a]	169.1 ± 32.8	162.5 ± 41.3
HbA_{1c} (%)[a]	8.1 ± 1.1	7.9 ± 1.4

Data are the mean ± SD.
[a] No statistical difference in any of these parameters between the 2 groups was observed.

2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 11 software (SPSS PC Inc, Chicago, Ill). All the data are expressed as mean ± SD, with the exception of Lp(a), CRP, and homocysteine, which were not normally distributed and are expressed as median and range. Paired Student *t* test was used for the within-groups comparison between baseline and the end of the study and independent Student *t* test was used for the comparison between groups for all the parameters studied, with the exception of Lp(a), CRP, and homocysteine, for which Wilcoxon signed rank test and Mann-Whitney *U* test were used, respectively. Bivariate correlation coefficients (*r*) were calculated using the Pearson product formula. A *P* value of less than .05 (2-tailed) was considered statistically significant.

3. Results

Baseline characteristics of the 2 groups are presented in Table 1. In the rosiglitazone group at the end of the 26-week period there were significant decreases of fasting plasma glucose, insulin, HbA_{1c}, and HOMA-IR levels vs baseline, as previously mentioned [18]. In contrast, in the control group, no significant changes in any of those 3 parameters were observed (Table 2).

As shown in Table 2, in the rosiglitazone group, total cholesterol and LDL-C presented an increase of about 6.5% to 8.5% at the end of the study, which was almost significant, whereas triglycerides and HDL-C remained practically unchanged. Moreover, both apo A-I and apo B were significantly decreased in the end of the study compared with baseline, and LDL–apo B ratio was significantly increased. Lipoprotein(a) and hs-CRP levels in the rosiglitazone group also presented significant reductions. In contrast, no significant differences in homocysteine were observed and fibrinogen presented a significant increase of about 20% with rosiglitazone. In the control group, none of the above parameters were changed from baseline to the end of the study.

In the rosiglitazone group, there were not any significant correlations between the change in HOMA-IR and the respective changes in apo A-I, apo B, LDL–apo B ratio, and fibrinogen levels. However, after logarithmic transformations of Lp(a) and CRP levels, their changes during rosiglitazone treatment were positively correlated with the respective change in HOMA-IR ($r = 0.498$, $P \leq .05$ and $r = 0.582$, $P < .05$, respectively).

As far as weight is concerned, in the rosiglitazone group there was a significant increase of about 1.6 kg at the end of the study. Body mass index was also increased but WHR was not, whereas in the control group these parameters remained unchanged. Bioimpedance analysis revealed a decrease of about 2% in body fat mass and an equal increase in body lean mass, as well as an increase of about 2.3 L in total body water with rosiglitazone, as shown in Table 3.

Table 2
Plasma glucose, plasma insulin, HbA_{1c}, lipids, and novel cardiovascular risk factors at baseline and the end of the study

	Rosiglitazone group (n = 20)			Control group (n = 20)			Rosiglitazone vs control
	Baseline	Week 26	*P*	Baseline	Week 26	*P*	*P*
Fasting glucose (mg/dL)	169.1 ± 32.8	135.8 ± 25.2	<.001	162.5 ± 41.3	157.8 ± 35.6	.54	<.001
Fasting insulin (μU/mL)	15.7 ± 5.3	13.2 ± 4.2	<.01	15.3 ± 7.9	15.9 ± 8.5	.71	<.01
HbA_{1c} (%)	8.1 ± 1.1	7.2 ± 0.9	<.001	7.9 ± 1.4	7.8 ± 1.2	.43	<.01
HOMA-IR	6.3 ± 1.8	4.4 ± 1.5	<.001	6.1 ± 2.3	6.2 ± 2.5	.63	<.001
Total cholesterol (mg/dL)	224.5 ± 31.0	238.8 ± 39.0	.06	233.1 ± 49.7	237.6 ± 42.2	.70	.07
Triglycerides (mg/dL)	137.9 ± 58.8	138.4 ± 50.4	.96	132.8 ± 45.3	135.1 ± 66.1	.65	.69
HDL-C (mg/dL)	54.9 ± 14.5	55.7 ± 15.3	.72	50.7 ± 23.6	52.7 ± 14.9	.66	.73
LDL-C (mg/dL)	142.3 ± 23.3	154.1 ± 34.4	.06	155.3 ± 20.7	157.7 ± 38.2	.52	.09
Apo A-I (mg/dL)	170.8 ± 33.0	153.5 ± 25.3	<.05	166.4 ± 37.2	165.9 ± 24.9	.49	<.05
Apo B (mg/dL)	123.3 ± 21.7	111.8 ± 25.5	<.05	118.6 ± 31.4	120.5 ± 23.3	.36	<.05
LDL–apo B ratio	1.17 ± 0.23	1.40 ± 0.22	<.001	1.31 ± 0.30	1.31 ± 0.25	.92	<.001
Lp(a) (mg/dL)	10.5 (8.9-54.1)	9.8 (8.0-42.0)	<.05	12.1 (8.1-46.9)	13.5 (6.4-63.1)	.58	<.05
Homocysteine (μmol/L)	11.8 (8.6-21.4)	12.5 (9.5-36.3)	.10	10.9 (7.5-31.8)	11.7 (8.3-27.9)	.22	.51
Fibrinogen (mg/dL)	303.5 ± 75.1	387.5 ± 70.4	<.01	312.9 ± 83.8	304.5 ± 75.8	.29	<.01
CRP (mg/dL)	0.33 (0.07-2.05)	0.25 (0.05-1.84)	<.05	0.35 (0.11-3.38)	0.42 (0.14-1.97)	.18	<.05

Data are the mean ± SD, with the exception of data for Lp(a), homocysteine, and CRP, which are expressed as median (range).

Table 3
Body weight, BMI, WHR, and bioimpedance analysis data at baseline and the end of the study

	Rosiglitazone group (n = 20)			Control group (n = 20)			Rosiglitazone vs control
	Baseline	Week 26	*P*	Baseline	Week 26	*P*	*P*
Weight (kg)	74.7 ± 9.1	76.3 ± 9.2	<.001	75.6 ± 8.1	76.1 ± 11.2	.38	<.01
BMI (kg/m^2)	27.4 ± 2.9	28.0 ± 3.0	<.001	27.6 ± 3.8	27.9 ± 3.4	.71	<.05
WHR	0.93 ± 0.07	0.92 ± 0.06	.24	0.95 ± 0.06	0.97 ± 0.07	.35	.09
Fat body mass (kg)	25.7 ± 7.2	24.8 ± 8.1	.08	27.5 ± 8.0	28.2 ± 8.7	.52	.06
Fat body mass (%)	34.5 ± 8.8	32.5 ± 9.5	<.01	36.4 ± 11.7	37.1 ± 10.4	.28	<.01
Lean body mass(kg)	49.0 ± 9.4	50.5 ± 10.4	.07	48.1 ± 8.8	47.9 ± 10.8	.73	.07
Lean body mass (%)	65.5 ± 8.8	67.5 ± 9.5	<.01	63.6 ± 11.7	62.9 ± 10.4	.47	<.01
Body water (L)	38.3 ± 6.0	40.6 ± 6.5	<.001	38.8 ± 7.7	38.6 ± 9.1	.68	<.01
Body water (%)	51.5 ± 6.8	53.5 ± 7.7	<.01	49.7 ± 8.2	49.3 ± 7.3	.54	<.01

Data are the mean ± SD.

As far as safety parameters are concerned, although a small reduction of 0.6 g/dL in hemoglobin levels has been observed in the rosiglitazone group, there was not any clinical or laboratory finding of anemia in any of the subjects throughout the study period. No subject had elevation of any liver function test above normal, or doubled the baseline values in the 2 groups. None of the subjects complained about leg edema or heart failure symptoms either.

4. Discussion

The present study is the first to evaluate the effect of a TZD on novel CVD risk factors in a population consisting of patients with both type 2 DM and hypertension. In particular, its aim was to determine whether add-on treatment with rosiglitazone in these patients would have a positive effect on Lp(a), CRP, homocysteine, and fibrinogen. Another purpose was to evaluate the effect of rosiglitazone on the levels of apo A-I and apo B of these patients. The main findings of our study are that rosiglitazone treatment was associated with significant reductions in Lp(a) and CRP levels, and a significant increase of fibrinogen without affecting homocysteine. Moreover, although we observed only an upward trend in total cholesterol and LDL-C, both apo A-I and apo B presented small significant reductions, and the LDL–apo B ratio was significantly increased.

This study has also some limitations that must be acknowledged. Basically, it was a nonrandomized, open-label, observational 6-month intervention study, with a small number of patients. The study population was selected, consisting of patients with established type 2 DM, as it was our intention to focus on the drug effect in patients for whom the drug is often used as add-on therapy, and therefore, the population had a relatively high degree of IR. The subjects were also hypertensive. Therefore, it is unknown whether a group with different characteristics would give similar results after rosiglitazone treatment. Finally, although bioelectrical impedance analysis is considered a reliable technique for body composition determination in various conditions, including DM, its values are affected by numerous variables and the interpretation of the results should be cautious [21].

Lipoprotein(a) consists of an LDL particle whose apo B-100 component is linked to apo(a), a protein with sequence homology to plasminogen [22]. Several studies have reported a positive graded association between Lp(a) levels and cardiovascular risk [23]. Most studies have not reported increased Lp(a) levels in type 2 diabetic patients [24,25]. However, Lp(a) is considered an independent risk factor for CVD in type 2 DM [26]. Troglitazone has been shown to increase Lp(a) in type 2 diabetic [27-29] and nondiabetic insulin-resistant subjects [30] in studies lasting up to 4 months. Although it was hypothesized that these findings should be a class effect [30], pioglitazone was not found to increase Lp(a) [31], but this was an open study with a rather small number of subjects (n = 8). In a randomized study in 118 diabetic patients, the addition of rosiglitazone resulted in about 15% increase in Lp(a) levels after 12 weeks of treatment [32]. In contrast to these findings, in the present study, Lp(a) levels presented a slight (about 9%) decrease with rosiglitazone, an observation suggesting that rosiglitazone could act beneficially on this factor. Apart from the possibility that different glitazones exert different effects on Lp(a), the inconsistency of these findings could be attributed to the relatively small number of subjects in most of the previously mentioned studies [26-31], along with the fact that until now commercially available tests for Lp(a) lack sufficient standardization and there is no consensus on how to best measure it; thus, reproducibility between laboratories is hampered [23,33]. Different commercial kits were used in the previously mentioned studies, a fact that could partially explain differences between baseline levels too. The relatively longer period of our study could also be an important factor for the observed differences. Longer and larger studies are necessary to clarify this issue.

A positive relationship between mild to moderate hyperhomocysteinemia and atherosclerosis has been reported in epidemiologic studies [23,34] and high homocysteine levels have been found in animal models of the metabolic syndrome [35]. To our knowledge, the effect of TZDs on

homocysteine has been reported only in an animal study, where troglitazone produced significant reductions in lean and fatty Zucker rats, a finding supporting the hypothesis that insulin is involved in hepatic homocysteine metabolism [36]. Our findings did not confirm these data because no change in total homocysteine levels were observed with rosiglitazone. It must be noted however that this study was possibly not powered to detect changes in homocysteine levels and further research on this issue is needed.

Several studies have consistently reported a positive association between plasma fibrinogen and the risk of future cardiovascular events; thus, fibrinogen is considered today as an independent marker of CVD risk [34,37]. Troglitazone did not alter fibrinogen concentration in type 2 diabetic patients in 2 previous studies [17,29]. In a double-blind study in nondiabetic patients with coronary artery disease, rosiglitazone reduced significantly fibrinogen vs placebo [38]. However, in our study, rosiglitazone was associated with a significant increase in fibrinogen. The inconsistency of these data could be merely attributed to a number of parameters, such as the different type of patients in the previously mentioned studies, the wide intraindividual variation in plasma fibrinogen levels over time [39], the inadequate standardization between different laboratory techniques [23], or the variation resulting from environmental factors; smoking cessation, increased exercise, or weight loss could reduce fibrinogen [23]. In our study, apart from the inevitable TZD-associated weight increase, all the previously mentioned factors remained stable throughout the study period, and the baseline and final evaluation took part in spring and autumn, respectively, to avoid seasonal variation in fibrinogen.

In general, an increase in fibrinogen levels could be either a result of a relative increase of its synthesis by the hepatocytes or a decrease in the fractional catabolic rate of the protein in the circulation, which under normal conditions is about 25% per day [40]. An increase in fibrinogen levels could reflect an inflammatory response [40], but this does not seem to be the case in the present study because CRP, another common inflammation marker, is reduced with rosiglitazone treatment. In the study of Sidhu et al [38], the reduction of plasma fibrinogen was attributed to the anti-inflammatory effects of rosiglitazone. However, the production and assembly of the different chains that form the molecule of fibrinogen in the liver is a rather complex procedure and in many cases increased hepatic fibrinogen production is not a part of the acute-phase response and occurs independently of the synthesis of other acute-phase proteins [41,42]. For example, in nephrotic patients the increased albumin synthesis is associated with an increase in fibrinogen synthesis and circulating levels [43]. Moreover, elevated fibrinogen synthesis and levels, in parallel to enhanced albumin synthesis to keep albumin levels within reference range, have been also reported in other conditions with increased plasma volume, even without a primary fall in serum albumin, such as hemodialysis patients [44] and individuals climbing from low to high altitude [45]. Thus, TZD-associated fluid retention [13], which is also documented in this study, as later discussed, through an increase in plasma volume could result in a net increase in fibrinogen production and levels, in spite a parallel anti-inflammatory effect. In addition, it has been shown that acute elevation of plasma glucagon in healthy humans stimulates fibrinogen secretion [46], and elevated glucagon and fibrinogen concentrations in type 2 diabetic patients are strongly correlated findings supporting that high glucagon levels are involved in increased fibrinogen production and hyperfibrinogenemia in type 2 DM [47]. Moreover, the main physiological inhibitors of glucagon release are probably hyperglycemia and hyperinsulinemia [48]; thus, their reversal could lead to an increase in glucagon levels. In the only study so far that evaluated the effect of a TZD in glucagon secretion, Gabriely et al [49] showed that during troglitazone treatment the glycemic threshold for secretion of glucagon in response to mild hypoglycemia was reset to a higher glucose concentration and the magnitude of the rise in glucagon concentration was significantly higher than in controls. In our study, glucagon concentration was not measured and therefore no direct evidence is available, but according to the above findings an elevation of glucagon secretion contributing to increase in fibrinogen levels cannot be excluded. Overall, it seems that more studies are necessary to clarify the effect of TZDs on fibrinogen levels, as well as the underlying mechanisms and the importance of this effect for the vasculature. Until such studies are available, one should interpret the data on this issue with caution.

Among the markers of inflammation that have been used to predict future risk of cardiovascular events, CRP seems to be the most important because in numerous studies CRP was found to be associated with an increased CVD risk independently of "traditional" risk factors [34,50]. All TZDs have been reported to reduce CRP levels in diabetic or nondiabetic subjects [29,38,51-54]. Our study confirms and extends these data because to our knowledge it is the second related study of such a long duration and the first to show a TZD-associated decrease in CRP in patients with type 2 diabetes and hypertension.

Numerous studies have investigated the effect of TZDs on lipid parameters in diabetic or insulin-resistant subjects. Troglitazone was found in various studies to be associated with decreases in plasma triglycerides, increases in HDL, and slight increases in LDL-C levels [14-16,29]. The last were accompanied with elevation in LDL particles' size [15,29] and increased resistance of LDL to oxidation [16]. Reductions in apo A-I were also reported [55], whereas apo B levels were not affected [14,16,55]. Pioglitazone was found in some studies to decrease triglycerides and increase HDL [56,57] and in others to also decrease total or LDL-C [51,56]. Data from rosiglitazone studies are less consistent. In most studies, rosiglitazone treatment resulted in increases

in total cholesterol, HDL-C, and LDL-C and no changes in triglycerides [32,58,59], but others found no changes in any of these parameters [60] or decreases in HDL and triglycerides [54,56]. In the study by Freed et al [59], apo A-I was reduced, apo B was slightly elevated, whereas the LDL–apo B ratio and relative flotation were increased with rosiglitazone monotherapy. These findings suggest an increase of the lipid content of LDL particles and a shift from small-dense to large-buoyant particles, which are more resistant to oxidation and therefore less atherogenic [59]. In our study, both total and LDL-C were elevated with rosiglitazone, and this change was almost significant, whereas triglycerides and HDL-C levels were not affected. In agreement with previous studies [55,59], we found a significant reduction in apo A-I. Apo B was also reduced and thus the LDL–apo B ratio was increased in the rosiglitazone group, something that further supports the increase in LDL lipid content and the shift from small to large particles with TZDs.

Rosiglitazone produced a significant increase of about 1.6 kg in weight and a respective increase in BMI. Weight gain of about this magnitude is a known side effect of all TZDs, noted in many previous studies [13,29,54,57-59]. Several factors have been proposed to be responsible for this, such as sodium and water retention, increased adipocyte differentiation possibly leading to alterations in fat mass, increased fatty acid uptake in adipocytes, reduced glucosuria, or the anabolic effects related to the better glycemic control [13,54,57,58,61]. To our knowledge, this study is the first to evaluate the effect of a TZD on weight in type 2 diabetic patients using bioimpedance analysis, which revealed a trend for reduction of body fat mass and increase of lean mass, as well as a highly significant increase in total body water in the rosiglitazone group. These data indicate that fluid retention is probably the most important mechanism for weight gain in this study. Moreover, in spite this increase in weight and BMI, WHR remained practically unchanged during rosiglitazone treatment, a finding suggesting that this weight gain was not connected with increases in visceral adipose tissue. In other studies, WHR was even found to be decreased after TZD administration [57,58]. A redistribution of fat with the use of TZDs from the visceral to the subcutaneous fat compartment, which is associated with lower cardiovascular risk, is supported from several studies measuring regional adiposity [12]. Overall, TZD-associated weight gain seems not to be connected with an increased cardiovascular risk.

In conclusion, this study demonstrated a significant reduction in Lp(a) and a significant increase in fibrinogen levels with rosiglitazone therapy for 26 weeks in patients with type 2 DM and hypertension, in contrast to other studies on these issues. It also confirmed previous data about CRP and apo A-I reductions and LDL–apo B increase, as well as water retention with the use of glitazones. Moreover, it was the first study to evaluate the effect of a TZD on homocysteine levels in humans, but did not found significant changes. The overall effect of rosiglitazone on cardiovascular risk factors seems positive, but large-scale trials are needed to clarify which of the novel factors are consistently affected from TZDs, as well as the possible clinical importance of these changes.

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