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Metabolic Effects of Rosiglitazone and Metformin in Greek Patients with Recently Diagnosed Type 2 Diabetes

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Abstract. *The aim of this study was to evaluate the comparative effects of rosiglitazone and metformin on metabolic parameters in recently diagnosed type 2 Greek diabetic patients. A total of 41 drug-naive individuals, with recently diagnosed type 2 diabetes, were randomized in 3 groups: DIET, diet alone; ROSI, diet plus rosiglitazone; and MET, diet plus metformin. Anthropometric indexes, blood pressure, hematological and biochemical parameters were estimated at baseline and after 18 weeks of treatment. We observed a significant decrease of fasting glucose (FBG) ($p<0.001$), glycated haemoglobin (HbA1c) (ROSI: $p=0.001$, MET: $p<0.001$), homeostasis model assessment for insulin resistance (HOMA-IR) (ROSI: $p=0.006$, MET: $p=0.009$) and glutamic pyruvic transaminase (SGPT) (ROSI: $p=0.004$, MET: $p=0.003$) in both ROSI and MET groups. Metformin significantly reduced fasting insulin ($p=0.04$), body weight ($p=0.026$), body mass index (BMI) ($p=0.022$), waist circumference ($p=0.022$) and gamma glutamyl transpeptidase (γ-GT) ($p=0.039$), while rosiglitazone decreased blood pressure (systolic: $p=0.05$, mean: $p=0.03$) and alkaline phosphatase (ALP) ($p=0.001$) compared to baseline values. Combined intervention with rosiglitazone and diet led to a slight, not significant, weight loss. Rosiglitazone and metformin are equaly effective in controling diabetes, decreasing insulin resistance and improving liver function. However, considering the more favorable effects of metformin on body composition and its documented cost-effectiveness, it seems to be preferable in newly diagnosed Greek diabetic patients.*

Growing evidence derived from previous clinical studies indicates that most of the available oral anti-diabetic agents are suitable for initial monotherapy in patients with type 2 diabetes (1-3). Metformin and thiazolidinediones (TZDs - rosiglitazone and pioglitazone) are well-documented insulin-sensitizing agents. Up to now, TZDs have been considered as more effective than metformin in decreasing insulin resistance (4-7). Besides this, numerous studies support the "pleiotropic" beneficial effects of TZDs on several (a) established cardiovascular risk factors such as lipids (8-10) and blood pressure (11-13) and (b) emerging cardiovascular risk factors such as cytokines, inflammatory markers (7, 14, 15), endothelial function (16-18) and pathogenetic mechanisms of atherosclerosis (19-21). Based on the above data, a number of investigators propose TZDs as first-line therapy in type 2 diabetes (2, 22). On the other hand metformin, apart from its hypoglycemic action, positively affects body weight, lipid profile, inflammatory markers, endothelial function and fibrinolytic process (23-27). Moreover there is a long-term (about 40 years) experience with metformin treatment in comparison to the relatively recent (aproximately 7 years) introduction of TZDs . Up to now a limited number of studies compared rosiglitazone and metformin directly and some of their results are still controversial (5, 7, 28-31). The most recent study which compared metformin and rosiglitazone, the ADOPT study, did not include Greek diabetic patients (32). Perhaps, this is of clinical importance because the greater part of Greek population presents different dietary habits in comparison with the rest European population (33, 34). Therefore, the aim of our study was the comparative evaluation of rosiglitazone and metformin influence on glycemic control and metabolic parameters in Greek patients with recently diagnosed type 2 diabetes, already being on dietary advice.

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Patients and Methods

Patients and research design. Individuals with recently diagnosed type 2 diabetes (<3 years), not on any anti-diabetic medication, were recruited from our out-patient diabetic clinic. Patients with renal and liver impairment or heart failure were excluded. According to the American Diabetes Association recommendations for medical

nutrition therapy, dietary instructions were provided to all participants by a registered dietitian (35). After 1 month of intensive dietary intervention, 48 patients (21 males and 27 females), still having fasting hyperglycemia (FPG>125 mg/dl), were randomly assigned to 3 groups: DIET (n=16), maintenance on diet alone; ROSI (n=16), diet plus rosiglitazone; and MET (n=16), diet plus metformin. Four patients in the DIET group stopped attending scheduled meetings due to personal reasons and they were excluded from the study. Moreover 1 metformin-treated (due to gastro-intenstinal discomfort) and 2 rosiglitazone-treated patients (due to amenorrhea with concomitant peripheral edema and intense weakness, respectively) discontinued treatment and they were also excluded. Finally 41 patients (17 males and 24 females), were eligible for all measurements: DIET (n=12, age 58.0±10.9 years, diabetes duration 16.1±20.5 months), ROSI (n=14, age 56.3±12.8 years, diabetes duration 30.7±31.3 months) and MET (n=15, age 57.8±9.1 years, diabetes duration 20.9±32.7 months). The duration of the study was 18 weeks, metformin and rosiglitazone dosages were gradually titrated (maximum doses 8 mg/dl for rosiglitazone and 1700 mg/dl for metformin) and our target was euglycemia. All concomitant medications (*e.g.* antihypertensives, lipid-lowering) remained unaltered throughout the study.

Clinical and laboratory measurements. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference was determined as the smallest girth between the lower rib margin and the iliac crest, at the end of a normal expiration. Systolic and diastolic blood pressures (SBP, DBP) were twice measured with a mercury sphygmomanometer. Before the first blood pressure examination all the participants were kept in a sitting position for at least 15 min. There was a 5 min interval between the 2 measurements and the mean value was estimated for the study's purposes. Mean blood pressure was calculated as SBP+2DBP/3.

Blood samples were obtained between 8 and 10 a.m. after an overnight fast. Haematological and biochemical parameters (haemoglobin, glucose, total cholesterol, triglycerides, high density lipoproteins-cholesterol (HDL-C), low density lipoproteins-cholesterol (LDL-C), creatinine, urea, uric acid, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (γ-GT) were measured enzymatically (Roche/Hitachi 912 automatic analyzer; Roche Diagnostics, Basel, Switzerland). Measurements of HbA1c were made by high-performance liquid chromatography (HA-8121 analyzer, Menarini, Italy). Plasma insulin was estimated by immunoradiometric assay (IRMA, Biosource, Belgium) and intra- and interassay coefficients of variation (CV) were 1.6% and 6.1%, respectively. Insulin resistance was estimated by homeostasis model assessment (HOMA-IR), calculated as fasting plasma insulin (μU/ml) X fasting plasma glucose (mmol/l)/22.5 (36, 37). All biochemical analyses were performed in our University Hospital Central Laboratory and all variables were measured at baseline and after 18 weeks of intervention. Taking into consideration the fluid retention and volume expansion in the ROSI group (38), the final results of all heamatological and biochemical measurements were adjusted to post-treatment changes in plasma volume as they were estimated by the hematocrit (Ht) alterations (hemodilution). As we noticed a 4% reduction in Ht, we considered equal reductions in all laboratory results and thereby we corrected the post-treatment values by multiplying by a 1.04 factor.

The study was approved by the institutional review board of the Aristotle University of Thessaloniki and conducted in accordance with the Helsinki Declaration. An informed consent was signed, after informing all participants about the research procedures.

Statistical analysis. SPSS 13.0 software (SPSS, Chicago, IL,USA) was used for statistical analysis. Data are presented as mean±SD. Normality of distribution was assessed by the Kolmogorov-Smirnov test. Data comparisons between groups were performed by Student's independent *t*-test and One Way ANOVA using LSD test. Baseline and post-intervention continuous variables were also compared within groups by paired *t*-test. The Pearson correlation coefficient was used for univariate analysis of all variables. All tests were two-tailed and a p-value<0.05 was considered to be significant.

Results

Baseline characteristics of all groups are presented in Table I. At baseline no significant differences were observed between groups in age, gender, duration of diabetes (One-Way Anova: F=0.982, p=0.385), clinical (body weight, BMI, waist circumference, blood pressure) and glycemic control parameters (HbA1c, FPG). All changes in studied variables are listed in Tables I and II and Figures 1 and 2. In response to rosiglitazone and metformin, HbA1c and fasting plasma glucose were significantly reduced (p<0.001). Both anti-diabetic regimens were associated with considerable reduction in calculated insulin resistance index – HOMA-IR (ROSI: p=0.006, MET: p=0.009) and in log-transformed HOMA-IR (ROSI: p=0.008, MET: p=0.003), as expected. Nevertheless, only metformin administration resulted in a significant (p=0.04) decrease in fasting insulin, while rosiglitazone tended to lower the latter parameter without reaching significance (p=0.093). Moreover, only metformin was associated with a significant reduction in body weight (p=0.026), BMI (p=0.022), and waist circumference (p=0.022) compared with baseline values. It is noteworthy that the decrease in waist circumference was independent of body weight alteration (r=0.078, p=0.800).

As shown in Table I and Figure 2, the rosiglitazone-treated group experienced a significant drop in systolic and mean blood pressure (p=0.05 and p=0.03, respectively). All groups showed slight but non-significant changes in lipid profile although metformin showed a more favourable effect. In particular, rosiglitazone increased all lipid parameters (total cholesterol, triglycerides, HDL-C, LDL-C) but not significantly (p>0.05). On the other hand, metformin decreased total cholesterol (p=0.349) and triglycerides (p=0.297) and increased HDL-C (p=0.153) and LDL-C (p=0.822) also not significantly.

Uric acid was significantly increased in the MET group (p=0.047) and decreased in ROSI and DIET groups (p=0.31 and p=0.044, respectively). SGPT activity showed marked reduction in both the ROSI (p=0.004) and MET

Table I. *Changes in response to treatment.*

Group	DIET			ROSI			MET		
	Week 0	change	*P*	Week 0	change	*P*	Week 0	change	*P*
HbA1c (%)	7.1±1.6	–0.6±1.8	NS	7.2±1.2	–1.0±0.7	**	7.8±1.1	–1.7±1.1	***
Fasting glucose (mg/dl)	137±19	9±47	NS	145±23	–26±18	***	162±31	–33±19	***
Insulin (μU/mL)	17.3±9.3	0.8±9.1	NS	21.7±7.0	–3.8±7.6	NS	24.8±14.8	–6.7±10.5	*
HOMA-IR	5.79±3.07	0.71±3.79	NS	7.89±3.33	–2.50±2.73	**	9.71±5.98	–4.01±4.67	**
LogHOMA-IR	0.70±0.24	0.05±0.31	NS	0.87±0.16	–0.17±0.20	**	0.92±0.25	–0.20±0.19	**
Weight (kg)	81.5±20.3	–0.9±2.1	NS	83.2±12.9	–0.3±3.3	NS	80.8±17.6	–2.5±3.5	*
BMI (kg/m^2)	29.6±4.6	–0.3±0.7	NS	31.0±4.5	–0.1±1.2	NS	30.8±3.1	–0.9±1.3	*
Waist circumference (cm)	105±11	–1.6±2.5	NS	107±11	–0.7±3.0	NS	109±9	–4.0±3.7	**
Systolic BP (mmHg)	127.2±15.1	–6.9±14.8	NS	133.4±16.2	–7.5±12.5	*	128.1±21.9	–0.4±9.9	NS
Diastolic BP (mmHg)	81.3±8.4	–1.3±9.2	NS	82.7±8.2	–2.3±6.6	NS	82.7±11.3	–1.92±8.5	NS
Mean BP (mmHg)	96.6±9.8	–3.2±8.5	NS	99.6±10.8	–4.1±5.9	*	97.8±13.8	–1.4±8.4	NS
Hb (g/dl)	14.1±1.1	–0.07±0.1	NS	14.4±1.9	–0.8±0.8	**	14.2±1.3	0.1±0.3	NS
Ht (%)	41.3±2.6	–0.04±0.6	NS	42.6±4.3	–1.6±2.0	*	42.3±3.0	–0.05±0.9	NS
Cholesterol (mg/dl)	205±33	12±45	NS	218±52	9±33	NS	232±44	–3±26	NS
Triglyceride (mg/dl)	148±77	21±64	NS	151±34	22±73	NS	191±135	–29±101	NS
HDL-C (mg/dl)	50±14	–4±7	NS	47±9	0.8±5	NS	46±9	1±3	NS
LDL-C (mg/dl)	125±30	12±36	NS	140±45	3±24	NS	148±29	1±17	NS
Uric acid (mg/dl)	5.5±1.2	–0.3±0.5	*	6.2±1.4	–0.4±1.4	NS	5.9±0.9	0.7±1.1	*
SGPT (U/L)	24±7	0.1±6	NS	26±10	–8±8	**	36±14	–12±12	**
γ-GT (U/L)	29±16	–4±5	*	23±16	–3±13	NS	43±30	–10±15	*
ALP (U/L)	74±12	4±19	NS	75±21	–12±11	**	76±20	2±13	NS

Data are means±SD. Paired-samples *t*-test was used. NS, not significant; *$p<0.05$; **$p<0.01$; ***$p<0.001$. HbA1c, glycated haemoglobin; HOMA-B%, homeostasis model assessment for β-cell function; HOMA-IR, homeostasis model assessment for insulin resistance; LogHOMA-IR, logarithmic transformation of homeostasis model assessment for insulin resistance; BMI, body mass index; BP, blood pressure; Hb, haemoglobin; Ht, hematocrit; HDL-C, high density lipoproteins-cholesterol; LDL-C, low density lipoproteins-cholesterol; SGPT, glutamic pyruvic transaminase; γ-GT, gamma glutamyl transpeptidase; ALP, alkaline phosphatase. DIET: diet; ROSI: diet + rosiglitazone; MET: diet + metformin.

($p=0.003$) groups. Besides this, γ-GT and ALP were reduced in MET ($p=0.039$) and ROSI ($p=0.001$) group, respectively. The aforementioned reduction in SGPT and ALP levels in the ROSI group were not related with body-weight alterations (r=0.075, $p=0.809$ and r=–0.182, $p=0.551$, respectively). Similarly in the MET group, we did not detect any association between weight loss and changes in SGPT (r=–0.067, $p=0.870$) or γ-GT (r=–0.034, $p=0.912$) activity.

As expected, only rosiglitazone administration significantly reduced Hb ($p=0.003$) and Ht ($p=0.022$), while metformin and diet yielded negligible changes (Table I). We noticed a 4% reduction in Ht, due to possible hemodilution, in the ROSI group. For this purpose we considered equal reductions in laboratory results and thereby we corrected the post-treatment values of HbA1c, FPG, HOMA-IR, logHOMA-IR total cholesterol, triglycerides, HDL-C, LDL-C, SGPT and ALP by multiplying by a 1.04 factor. After the adjustment, we re-assessed the changes of the above variables (Table II) and we realized a further increment of all lipid parameters

Table II. *Correction of changes in ROSI group according to hemodilution.*

Group	ROSI		
	Week 0	change	*P*
HbA1c (%)	7.1±1.2	–0.7±0.8	**
Fasting glucose (mg/dl)	145±23	–21±19	***
HOMA-IR	7.89±3.33	–2.28±2.75	*
LogHOMA-IR	0.87±0.16	–0.15±0.21	*
Cholesterol (mg/dl)	218±52	18±34	NS
Triglyceride (mg/dl)	151±34	29±76	NS
HDL-C (mg/dl)	47±9	2±5	NS
LDL-C (mg/dl)	140±45	9±25	NS
SGPT (U/L)	26±10	–7±8	**
ALP (U/L)	75±21	–10±11	**

Data are means±SD. NS, not significant; *$p<0.05$; **$p<0.01$; ***$p<0.001$. HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model assessment for insulin resistance; LogHOMA-IR, logarithmic transformation of homeostasis model assessment for insulin resistance; HDL-C, high density lipoproteins-cholesterol; LDL-C, low density lipoproteins-cholesterol; SGPT, glutamic pyruvic transaminase; ALP, alkaline phosphatase.

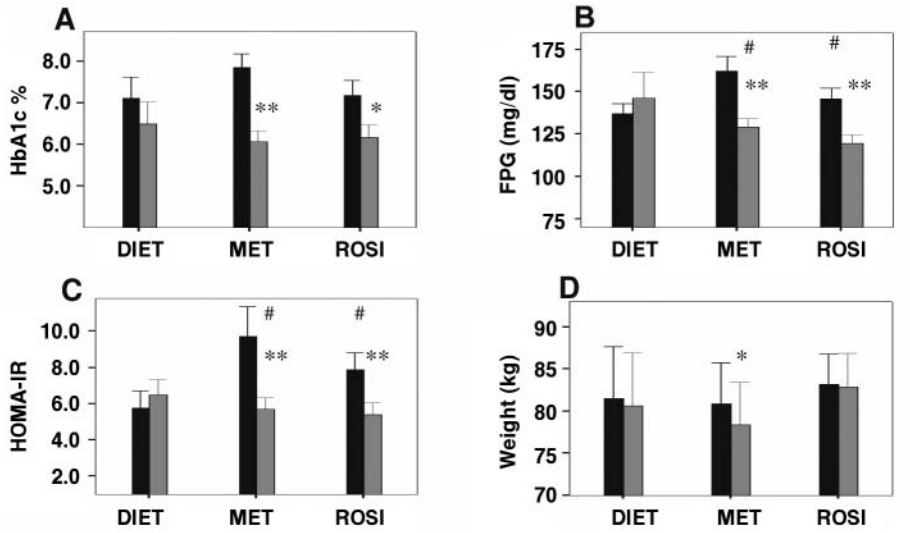

Figure 1. *Effect of the treatment on: (A) HbA1c, glycated haemoglobin; (B) fasting glucose; (C) HOMA-IR, homeostasis model assessment for insulin resistance; (D) weight. Values are means±SD. *p<0.05; **p<0.001 (p-values of levels of variables between baseline versus the end of the study within groups). #p<0.05 (Post-hoc analysis of changes of variables between groups). DIET: diet; ROSI: diet + rosiglitazone; MET: diet + metformin.* ■ *before treatment;* ■ *after treatment.*

(total cholesterol, triglycerides, HDL-C, LDL-C) without approaching significant levels ($p>0.05$). On the other hand, the hematocrit-related correction attenuated the rosiglitazone-induced reductions in HbA1c ($p=0.004$), FPG ($p=0.001$), HOMA-IR ($p=0.011$), logHOMA-IR ($p=0.023$), SGPT ($p=0.007$) and ALP ($p=0.007$). However, the above differences remained significant.

Discussion

The aim of the present randomized, controlled study was to compare the effects of pharmaceutical and dietary interventions on newly diagnosed, drug naive Greek patients with type 2 DM. Up to now there are conflicting results concerning the differential effect of several anti-diabetic agents on drug naive diabetic patients with poor glycemic control (3). Rosiglitazone, as initial therapy, was found to improve glycemic control similarly to metformin in some studies (7, 39), while in others it was proved to be less effective (5, 28, 31). The ADOPT study (32) was an international multicenter study of glycemic durability of rosiglitazone, metformin and glyburide after 4 years of treatment. Within the first 18 weeks of the ADOPT study, the results of rosiglitazone and metformin comparison were similar to our results. Rosiglitazone and metformin had the same beneficial effect on fasting glucose, HbA1c and insulin resistance. Moreover metformin significantly reduced body weight and waist circumference. After the study completion (within 4 years), glycemic durability was preserved in more rosiglitazone treated patients (85%) in comparison with metformin-treated ones (79%). However, the choice of time to failure in the maintenance of adequate glycemic control based on a confirmed fasting glucose level of more than 180 mg/dl , rather than on HbA1c levels. HbA1c is the measure of glycemia that correlates best with the risk of complications and has been used as the metabolic target for therapy for more than a decade (40). Despite the reduction in time to failure, according to the fasting glucose, the HbA1c results suggest a clinically less impressive effect. The mean HbA1c level at 4 years was 0.13 less in the rosiglitazone group than in the metformin group. Similarly, the fraction of the study cohort that was still receiving its assigned treatment and had a HbA1c level of less than 7% was only 4% higher in the rosiglitazone group than in the metformin group (40% *vs.* 36%). Although these differences are statistically significant, the relatively small difference in HbA1c levels achieved over 4 years in the rosiglitazone group as compared with the metformin group is of questionable clinical significance (41). Moreover, rosiglitazone treatment was associated with LDL-C increase, significant weight gain, more edema (14.1% *vs.* 7.2%) and increased use of loop diuretics and statins than metformin-treated patients. Our study only concerns Greek type 2 diabetic patients and this is the main difference from ADOPT study, taking into consideration the shorter duration and the smaller number of patients. Perhaps, this is of clinical importance because the greater part of Greek population presents different dietary habits in comparison with the rest European population like small breakfast and heavy lunch (33).

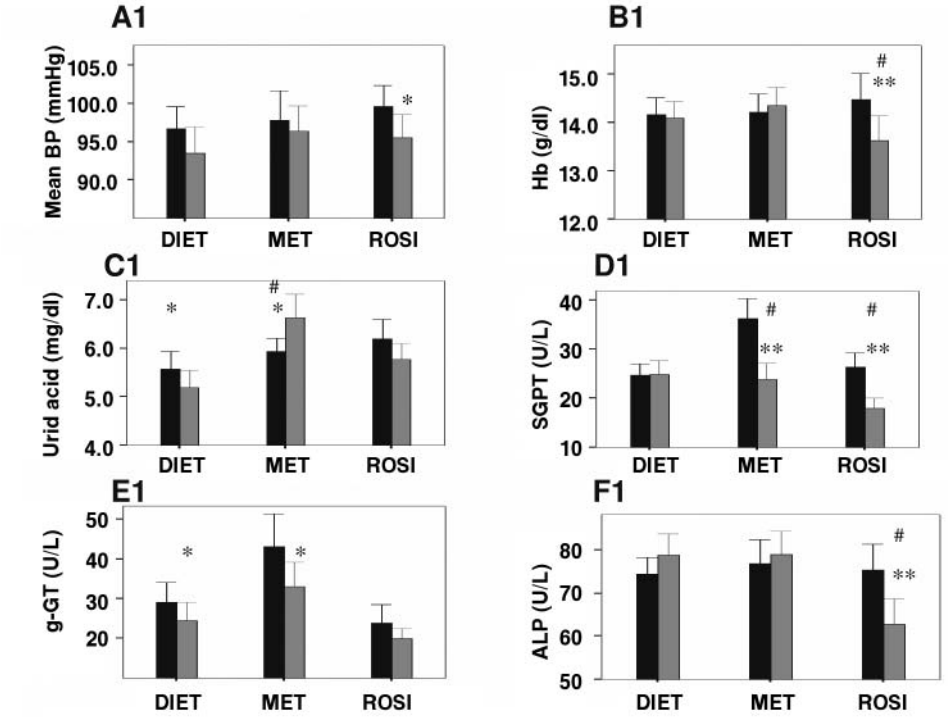

Figure 2. *Effect of the treatment on: (A1) mean BP, blood pressure; (B1) Hb, haemoglobin; (C1) uric acid; (D1) SGPT, glutamic pyruvic transaminase; (E1) γ-GT, gamma glutamyl transpeptidase; (F1) ALP, alkaline phosphatase. Values are means±SD. *p<0.05; **p<0.001 (p values of levels of variables between baseline versus the end of the study within groups). #p<0.05 (Post-hoc analysis of changes of variables between groups). DIET: diet; ROSI: diet + rosiglitazone; MET: diet + metformin.* ■ *before treatment;* ■ *after treatment.*

Our findings support the notion that these 2 agents show almost equal anti-hypoglycemic activity, metformin being slightly superior, something we could explain after taking into consideration the higher HbA1c baseline levels in the MET group (42).

We demonstrated that rosiglitazone reduced insulin resistance equaly to metformin, causing a slight discordance of opinion with several investigators who suggested that TZDs improve insulin sensitivity to a greater extent than metformin (5-7, 43). However, we must take into consideration that HOMA-IR is a basal state index of insulin resistance in the fasting state, which can't distinguish hepatic from peripheral insulin resistance (37).

Obesity constitutes a predominant pathogenetic factor of insulin resistance leading to increased incidence of type 2 diabetes (44). Central obesity, easily estimated by the waist circumference, is closely associated with type 2 diabetes development, all the more independently of the BMI (45). Numerous studies measuring regional adiposity support the notion that visceral fat has a prevalent role in the development of diabetic metabolic disorders, compared with subcutaneous fat (46). In our study, metformin plus diet therapy produced a significant reduction in waist circumference, body weight and BMI, which is of great clinical importance. In addition the metformin-induced waist circumference reduction was independent of weight loss, which leads to the conclusion that metformin not only confers beneficial effects on body weight reduction, but also on fat distribution, in agreement with the literature (47). On the other hand, combined intervention with rosiglitazone and diet led to a slight weight loss. In comparison to DIET group, which showed a more pronounced weight reduction, rosiglitazone treatment led to weight gain but to a lesser extent than mentioned in previous reports (38). This could be attributed to the short duration of our study. Moreover, despite the undesirable weight gain after rosiglitazone treatment, several studies support its favourable effect on fat distribution (*i.e.* visceral fat decrease) (5, 38).

Nowadays the positive relationship between hypertension and insulin resistance is well known (48). Although metformin and rosiglitazone are equally effective in insulin resistance reduction, we found different effects on blood pressure, in agreement with previous reports (11, 12, 49-51). We confirmed that rosiglitazone lowers systolic and mean blood pressure (11, 12, 51), while metformin shows negligible effect on them (11, 49, 50). Perhaps, metformin-induced vascular effects are not involved in blood pressure regulation (52).

Numerous studies investigated the effects of TZDs on lipid parameters; most of them have reported positive effects (8-10). In our study, metformin compared to rosiglitazone, showed a more favorable effect on cholesterol, TRG, HDL-C, LDL-C, but these changes were not significant. Perhaps pioglitazone favors lipid profile more than rosiglitazone (10).

As expected, rosiglitazone resulted in a considerable reduction in Hb. This is of clinical relevance, especially in subjects with marginal values of Hb or anemia. Fluid retention and plasma volume expansion are probably the most important mechanisms involved (38, 53). However, according to recent reports we can not rule out a suppressive effect of rosiglitazone on the bone marrow (54). We also estimated the influence of hemodilution on biochemical parameters, but the resulting change was small and not significant. To our knowledge, this is the first study taking into consideration hemodilution for interpreting measured parameters. Although differences in our study were not significant, it would be better for other studies using TZDs to consider correcting their values according to the magnitude of hemodilution, in order to eliminate possible variations.

There are several studies referred on the effect of metformin on serum urate levels, but their results are not consistent (55). In some of them, metformin lowered serum urate levels (55). Since hyperuricaemia is a frequent finding if insulin resistance is present, the increment in uric acid after metformin-induced reduction of insulin resistance, was a surprising finding in our study. It is plausible that a small increase in lactic acid concentration may antagonize the renal excretion of uric acid, leading to elevated serum urate levels.

Fatty liver (hepatic steatosis) is associated with hyperglycemia and several factors coexisting with insulin resistance syndrome, like obesity and hyperlipidemia 56. Increased concentration of serum and liver fatty acids induces overproduction of triglycerides. Hepatic fat deposition develops when triglycerides secretion as very low density lipoproteins (VLDL) can not counterbalance their production. Fatty liver is a common characteristic among diabetic patients (50-70%), usualy without symptoms. Mild laboratory abnormalities (ALP, transaminases, γ-GT elevation) are detected in 18% of the diabetic population (57). In our study, both rosiglitazone and metformin improved all biochemical markers of liver function, independently of body weght, BMI and waist circumference changes suggesting reduced deposition of fat in liver.

Among all anti-diabetic drugs only metformin has been proved to reduce cardiovascular events (58). According to the UKPDS study (58), metformin decreased all diabetes-related events (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction) by 32%, diabetes-related mortality by 42% and all-cause mortality by 36% in an overweight and obese diabetic population. In comparison with the diet-group, metformin also elicited a 39% reduction of acute myocardial infarction risk and a 30% reduction of all cardiovascular events. Contrary to metformin, a recent meta-analysis of treatment trials of rosiglitazone (59) showed that rosiglitazone was associated with a significant increase in the risk of myocardial infarction (odds ratio, 1.43; 95% confidence interval [CI], 1.03 to 1.98; $p=0.03$) and a borderline-significant finding for death from cardiovascular causes (odds ratio, 1.64; 95% CI, 0.98 to 2.74; $p=0.06$). Thus, this meta-analysis has raised substantial uncertainty about the cardiovascular safety of rosiglitazone (60). Apart from these advantages metformin seems to be a cost effective regimen (61), considering that in Greece, its monthly cost treatment (1700 mg/day) is 14 times lower than that of rosiglitazone (8 mg/day) one.

The present study has limitations. Despite the small number of patients, the sample group was sufficiently homogeneous. We attempted to limit drug influences and for that purpose we included patients who had not received any oral anti-diabetic agent. Therefore, it is unknown if the same intervention would confer similar results in a group with different characteristics. To calculate insulin resistance, we used homeostasis model assessment (HOMA-IR), a basal state method. So the interpretation of insulin resistance values must be cautious. Finally, the duration of the study was relatively short, since some studies concerning pioglitazone support the notion that maximum action of TZDs appears later (sometimes after almost a year) compared with other antidiabetic agents (62).

In conclusion, rosiglitazone and metformin improve glycemic control, insulin resistance and hepatic biochemical parameters to a similar degree in drug naive Greek patients with recently diagnosed type 2 DM. In addition, rosiglitazone reduces blood pressure, while metformin exerts more favourable effects on body weight and fat distribution. However, metformin as a cost-effective regimen with documented positive effect on cardiovascular risk reduction, seems to be preferable as initial treatment in newly diagnosed Greek patients with type 2 DM.

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