Evaluation of Rosiglitazone Administration on Cardiovascular Function in Severe Obesity

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ABSTRACT

Background: Obese patients have myocardial structural and functional alterations related to insulin resistance. **Hypothesis:** The purpose of the study was to analyze the effects of rosiglitazone, an insulin sensitizer agent, on cardiac morphometry and functioning.

Methods: In 2 groups of sex- and age-matched, nondiabetic, obese patients (5 men and 7 women, age 19–51 y; group A: body mass index [BMI] 40.6 ± 3.4 kg/m²; group B: BMI 42.6 ± 2.7 kg/m²), we evaluated the basal insulin sensitivity index (HOMA[IS]), body composition by bioelectrical impedance analysis and 24-h blood pressure monitoring. Furthermore, all patients underwent conventional 2-Dimensional and color Doppler echocardiography, and pulsed-wave tissue Doppler imaging (TDI). After the baseline evaluation, all patients were put on a hypocaloric diet (70% basal metabolic rate) plus placebo if they were in group A, or plus rosiglitazone (4 mg twice daily; Avandia [GlaxoSmithKline plc., Brentford, Middlesex, United Kingdom]) if they were in group B, for 6 mo.

Results: Significant decreases in body weight, total fat mass, BMI, and systolic blood pressure were registered in both groups. Rosiglitazone administration appeared more efficient in improving HOMA[IS] (mean difference: 0.30 ± 0.19 versus 0.11 ± 0.21 , $p < 0.05$). Left ventricular (LV) diastolic diameter (49.4 ± 7.7 versus 52.3 ± 5.4 mm, $p < 0.05$) and E wave (0.89 ± 0.18 versus 0.99 ± 0.20 m/sec, $p < 0.05$) increased in the rosiglitazone group due to a rise in preload and water content without peripheral edema. The increase in systolic (Sa) wave velocity in both groups was probably a result of the general improvement in insulin metabolism and the decrease in blood pressure.

Conclusions: We confirmed the positive effect of rosiglitazone on glucose metabolism in obese, nondiabetic patients, but changes in insulin sensitivity did not explain the cardiac effects produced by further mechanisms.

Key words: obesity, left ventricular function, rosiglitazone, tissue Doppler imaging

Introduction

Rosiglitazone, a peroxime proliferator-activated receptor (PPAR_γ) agonist, improves cardiac insulin sensitivity and left ventricular (LV) function in animal studies. In diabetic patients, better control of diastolic blood pressure was reported, whereas the effects on left ventricular mass (LVM) and other cardiovascular function indexes have not been clearly demonstrated.^{1–2} A recent meta-analysis of treatment trials of rosiglitazone showed that a significant increase in the risk of myocardial infarction and death from cardiovascular causes,³ and edema or congestive heart failure, may occur in diabetic patients with cardiac dysfunction.⁴

In obese patients, insulin resistance is one of the mechanisms involved in hypertrophy and in LV remodeling that can be involved in diabetic cardiomyopathy. In fact, although LV hypertrophy has been classically viewed as an adaptive response of the cardiovascular system to an

increased load, the progressive accumulation of myocardial fatty acids, associated with insulin resistance, leads to myocardial contractile dysfunction in obesity and might be an early marker of heart disease. A relation between body mass index (BMI) and noninvasive indexes of diastolic function was recently confirmed in young, obese women using a tissue Doppler imaging (TDI) technique.⁵ Study of mitral annulus by TDI is a relatively load-independent means of analyzing systolic and diastolic function.

The aim of this study was to evaluate the effects of rosiglitazone in association with a hypocaloric diet on echocardiographic, Doppler, and TDI indexes of systolic and diastolic LV function in severe, uncomplicated, obese patients. We wanted to evaluate if the improvement in insulin sensitivity after the administration of rosiglitazone produces beneficial effects on cardiovascular parameters, a possible LV remodeling in obesity, or if it is followed by an increase in some risk factors for heart failure.

Methods

We studied 24 obese patients without endocrine diseases, diabetes (blood glucose <7.0 mmol/L, in line with the American Diabetes Association criterion), liver or renal dysfunction, hypertension ($>140/90$ mm Hg), anamnesis and signs of coronary disease by standard 12-lead electrocardiogram (ECG), or previous congestive heart failure. Body weight had been stable during the previous 6 mo. Written informed consent was obtained from all subjects, and the protocol was approved by the Local Ethical Committee. Patients, divided into 2 groups, were matched for sex, age, BMI, and blood glucose and insulin plasma levels (see Table 1). After overnight fasting, body composition was determined by bioelectrical impedance analysis (Akern, Firenze, Italy), and patients with fluid overload according to vectorial analysis were excluded.⁶ Indirect calorimetry (Sensor-Medics, Milano, Italy) was also determined to evaluate basal metabolic rate (BMR). A 24-h ambulatory blood pressure monitoring was conducted with Spacelabs model 90207 (Spacelabs Medical, Radmont, Wash., USA). After baseline evaluation, all patients received a hypocaloric diet (18% proteins, 58% carbohydrates, and 24% lipids) set at about 70% of their BMR and were randomly assigned to receive either placebo (twice daily), if in group A, or rosiglitazone (4 mg twice daily; Avandia [GlaxoSmithKline plc., Brentford, Middlesex, United Kingdom]) if in group B. Studies with thiazolidinediones (TZDs) in obese, nondiabetic patients are still limited, and 4 mg twice daily has proven to be effective for lipid and glucose metabolism in diabetic patients.

Insulin sensitivity was calculated using the basal insulin sensitivity index (HOMA[IS]) as $\text{HOMA[IS]} = 22.5 / [\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)}]$ as described by Matthews et al.⁷

Two-Dimensional and 2-Dimensionally directed M-mode echocardiographic parameters were obtained with a Vingmed System 5 instrument (GE Medical Systems, Milwaukee, Wisc., USA). Parasternal long- and short-axis views and apical 2- and 4-chamber views were used for evaluating LV and valvular function with a multifrequency sector transducer. Measures were obtained according to the American Society of Echocardiography (ASE) recommendations, and significant valvular disease was excluded. Left ventricular mass was calculated by the Devereux formula: $0.8 \times [1.04 \times (\text{LV diameter} + \text{septum} + \text{posterior wall})]^3 - [(\text{LV diameter})^3 + 0.6]$.⁸ Normalization by height^{2.7} was used. The hypertrophy index (HI) was calculated by the formula (interventricular septal wall thickness in diastole [IVSD] + LV posterior wall dimension [LVPWD])/LV diastolic dysfunction (LVDD). Pulsed- and continuous-wave Doppler examinations were conducted with a 2.5-MHz probe. Isovolumic relaxation time (IVRT) was recorded from the apical 4-chamber view by simultaneous recording of LV outflow tract and mitral flows. The pulsed-wave spectral mode was used for the TDI study; a 5-mm sample volume was placed at

the lateral border of the mitral annulus. Conventional mitral inflow Doppler was studied for 5 consecutive beats with the sample volume placed at the tips of mitral leaflets. Systolic (Sa), early (Ea), and late (Aa) diastolic velocities were measured. After 6 mo of treatment, the evaluation was repeated. All recordings were done by 2 experienced echocardiographers who were blind to the previous measurements and to drug treatment.

Statistical Analysis

Results are presented as means $\pm$ standard deviations (SDs). Changes from baseline were assessed by the paired *t* test for each variable. Differences between the 2 groups were evaluated by the unpaired *t* test. Pearson's correlation coefficient was used to investigate the relationship between change in HOMA(IS) and significant variation in echocardiographic parameters. A *p*-value <0.05 was considered statistically significant. Statistical analysis was conducted with the SPSS package version 12.0 (SPSS Inc., Chicago, Ill., USA).

Results

At the end of the study, we registered a significant decrease in body weight, total fat mass, and BMI in both groups, whereas a significant increase in water content was registered only in the rosiglitazone group without clinical signs of edema (Table 1).

Hypocaloric diet significantly reduced blood glucose and insulin plasma levels, but rosiglitazone was more effective on HOMA(IS) (mean differences: 0.30 ± 0.19 versus 0.11 ± 0.21 , $p < 0.05$). Furthermore, triglycerides and free fatty acids (FFAs) plasma levels decreased significantly in both groups without differences between treatments (Table 1).

Hematological parameters and renal function did not register any significant change in either group.

Mean 24-h systolic blood pressure decreased, with similar behavior in both groups (mean differences: systolic -7.9 ± 2.9 versus -5.8 ± 3.7 mm Hg); no change was registered for mean diastolic 24-h blood pressure.

Even if obese patients may pose difficulties in echocardiographic studies, measurement of TDI and pulsed Doppler flow was always of good quality. At baseline, no significant differences were found between the 2 groups in echocardiographic parameters. After 6 mo, we registered a significant increase in Sa in both groups (mean differences: diet 0.014 ± 0.011 versus rosiglitazone 0.020 ± 0.022); whereas LVDD and E-wave velocity increased only in rosiglitazone-treated patients (Table 2). Furthermore, the changes in HOMA(IS) did not appear to correlate with the changes in LVDD ($r = 0.087$, $p = 0.692$), E ($r = -0.014$, $p = 0.949$), and Sa ($r = -0.216$, $p = 0.312$).

Discussion

In a group of obese, hyperinsulinemic, normoglycemic patients, a hypocaloric diet induced significant weight loss

TABLE 1: Clinical and biochemical parameters (mean±SD) during the study

	Group A (n = 12, 7 F/5 M) (diet + placebo)		Group B (n = 12, 7 F/5 M) (diet + rosiglitazone)	
	Baseline	After 6 mo	Baseline	After 6 mo
Age (y)	36.5±8.1		31.4±11.6	
Body weight (kg)	109.7±10.5	99.9±7.1*	115.5±17.9	103.9±15.6*
BMI (kg/m ²)	40.6±3.4	37.0±3.0*	42.6±2.7	38.4±3.0*
WHR	0.898±0.091	0.913±0.064*	0.897±0.083	0.902±0.084*
Fat mass (kg)	48.1±6.4	40.6±8.1*	52.2±8.8	39.6±13.1*
Water (% of body weight)	43.3±6.7	43.9±6.5	40.1±3.3	41.9±3.8*
Systolic BP (mmHg)	129±9	121±11*	130±10	124±9*
Diastolic BP (mmHg)	75±7	79±6	75±9	78±8
Hemoglobin (g/dl)	14.1±1.4	13.9±1.3	14.6±1.2	14.2±1.4
Hematocrit (%)	41.8±4.0	42.1±3.6	43.4±3.2	42.5±3.7
Blood urea nitrogen (mg/dl)	29.1±5.3	29.3±4.6	29.2±6.6	30.3±5.4
Creatinine (mg/dl)	0.8±0.2	0.8±0.2	0.8±0.2	0.9±0.1
Na ⁺ (mEq/l)	140.3±1.7	140.1±1.5	139.8±2.1	140.5±1.9
Total protein (g/dl)	7.1±0.3	7.1±0.4	7.3±0.3	7.0±0.5
Glucose (mmol/l)	5.0±0.6	4.6±0.4*	4.6±0.3	4.4±0.4*
Insulin (μU/ml)	13.1±4.9	9.8±2.4*	13.6±5.4	7.9±2.3*
HOMA (IS) ^a	0.416±0.211	0.528±0.131*	0.426±0.190	0.728±0.259*
Triglycerides (mg/dl)	132.1±49.7	108.5±36.5*	108.4±25.2	80.3±29.6*
FFA (mg/dl)	657.3±159.8	490.7±126.9*	723.0±111.5	577.0±204.5*

*p<0.05 versus baseline; ^a unpaired *t* test between the differences of the 2 groups, p<0.05. *Abbreviations:* BMI = body mass index; BP = blood pressure; F = female; FFA = free fatty acid; HOMA(IS) = basal insulin sensitivity index; M = male; SD = standard deviation; WHR = waist to hip ratio.

and reduction in systolic blood pressure, blood glucose, and insulin plasma levels. Adding rosiglitazone further improved insulin sensitivity, but also produced an increase in LVDD and E-wave velocity. Both of these effects might have been a result of the increase in fluid retention previously registered with TZDs. Furthermore, we registered an increase in Sa wave velocity, similar between diet and rosiglitazone treatment groups, probably due to the general enhancement in insulin metabolism and the decrease in systolic blood pressure.

Recently, myocardial and functional alterations in obese subjects were demonstrated secondary to LV volume overload, and to insulin resistance and FFA metabolism (uptake and utilization), because as a growth factor for the myocardium, insulin produces sodium retention and volume expansion, as well as sympathetic nervous system activation, and increases pressor response to angiotensin II.

The possible development of pharmacological compounds that can reverse the metabolic and cellular remodeling mechanisms by reducing insulin resistance is under debate. Animal studies have shown that TZDs have a favorable effect, preventing the increase in LV mass, but unfortunately, these effects have not been confirmed in human studies.⁹ On the contrary, rosiglitazone administration was reported to produce congestive heart failure in susceptible patients, probably by increasing the intravascular volume for a critical role in the regulation of sodium balance¹⁰ and oxygen demand.¹¹

In our study, after 6 mo of a hypocaloric diet, we obtained significant weight loss and decreases in blood glucose and insulin plasma levels. Rosiglitazone increased insulin sensitivity more than did diet alone. The results for glucose metabolism confirmed those obtained by other authors.¹² We also registered a decrease in triglyceride and FFA

TABLE 2: Echocardiographic parameters (mean±SD) during the study

	Group A		Group B	
	baseline	6 mo	baseline	6 mo
Morphometric indexes				
LVDD (mm)	50.8±5.3	51.8±3.8	49.4±7.7	52.3±5.4*
LVSD (mm)	31.3±4.6	33.8±3.1	31.7±6.7	33.1±4.0
IVSD (mm)	11.3±2.9	11.0±1.5	11.7±1.6	11.5±1.5
LVPWD (mm)	10.7±1.8	10.8±1.5	11.2±1.5	10.8±0.9
Hypertrophy index	0.43±0.07	0.43±0.05	0.48±0.11	0.43±0.05
LVM/height (gr/h ^{2.7})	56.9±20.6	59.9±12.6	60.1±13.1	58.8±14.8
Functional and Doppler				
EF (%)	67.8±53.0	63.1±32.0	68.9±50.1	66.1±40.2
IVRT (ms)	73.0±14.5	74.9±13.1	74.7±10.0	65.0±13.1
E (m/s)	0.80±0.15	0.86±0.11	0.89±0.18	0.99±0.20*
A (m/s)	0.67±0.12	0.65±0.07	0.69±0.17	0.70±0.13
E/A	1.22±0.25	1.33±0.21	1.37±0.45	1.44±0.30
DT (msec)	230±36	215±25	204±28	201±35
Sa (m/s)	0.090±0.017	0.104±0.013*	0.096±0.022	0.116±0.024*
Ea (m/s)	0.143±0.131	0.155±0.030	0.161±0.036	0.180±0.035
Aa (m/s)	0.103±0.022	0.107±0.022	0.113±0.034	0.110±0.033
E/Ea	5.8±1.5	5.8±1.2	5.6±0.9	5.0±1.2
Ea/Aa	1.5±0.6	1.6±0.5	1.6±0.8	1.8±0.6

* $p < 0.05$ versus baseline. *Abbreviations:* Aa = late diastolic wave velocity; DT = deceleration time; Ea = early wave velocity; EF = ejection fraction; LVDD = left ventricular diastolic dysfunction; LVM = left ventricular mass; LVPWD = left ventricular posterior wall dimensions; IVRT = isovolumic relaxation time; Sa = systolic wave velocity.

plasma levels; this was not confirmed by all authors.¹³ Weight loss can be achieved during rosiglitazone treatment when associated with nutritional counseling; nevertheless, fluid retention and peripheral edema formation have been frequently reported. The exact mechanism of these phenomena is still uncertain. It was recently demonstrated in Zucker rats that rosiglitazone increases vascular permeability and the expression of vascular endothelial growth factor in adipose tissue, but not in heart and skeletal muscle.¹⁴ Furthermore, it was suggested that insulin sensitivity may not be an essential factor for TZD to induce edema. In line with this result, in obese, nondiabetic subjects, the effect of rosiglitazone on capillary permeability was not nitric oxide-dependent, and showed no correlation between plasma volume expansion and the vascular action of insulin.^{15,16} We found a significant increase in total water content in rosiglitazone-treated patients, even if clinically

evident edema was not present and no significant imbalance in Na⁺ content was recorded. On the contrary, we registered a significant reduction in systolic blood pressure that was similar in the 2 study groups. A possible explanation is the direct suppressing effect of TZD on intracellular Ca²⁺ or the angiotensin II receptor in vascular smooth muscle cells,¹⁷ or by renal Na⁺ reabsorption in the collecting duct.¹⁰

Only 3 cardiac parameters were different from baseline at the end of the study. Left ventricular diastolic dysfunction increased in treated patients, probably for fluid retention, as documented by the increase in total body water. Also E-wave velocity increased, and once again, because early diastolic filling is related to LV-filling pressure, this can be explained by the increase in water percentage. Similarly, Sa that represents mitral annulus systolic velocity and reflects the peak velocity of longitudinal fiber shortening during systole increased in all patients. Even if TDI values

are looked at as relatively load-independent indexes of myocardial function, a recent study demonstrated that there is a preload dependence of Sa, which increases linearly with preload.¹⁸ We do not have the possibility to discriminate intravascular from extravascular fluid retention; nevertheless, the increase in circulating volume (i.e., of the preload) improves systolic performance and is consistent with Sa improvement. Afterload decrease, documented by the decrease in blood pressure, may explain the Sa increase in those in the placebo group who did not experience fluid retention.¹⁹ Systolic wave velocity is directly related to ejection fraction, which did not change; this is not surprising because Sa is more sensitive than ejection fraction in the measurement of systolic function. The Sa may also reflect an increase in contractility; indeed, it has been demonstrated that reduced myocardial efficiency is an early abnormality in the hearts of obese mice and precedes the onset of hyperglycemia.²⁰ The improvement in insulin sensitivity in both study groups also supports this possible explanation.

Limitation of the Study

The study may have been biased by the small sample size and the short observation period, which could have reduced the significance and the burden of clinical effects. Large clinical trials were inconclusive regarding the effect of rosiglitazone on the overall risk of cardiovascular diseases, and the only documented effect (albeit not fully understood) is that rosiglitazone might increase the risk of heart failure.²¹ Our results confirmed that patients treated with rosiglitazone need careful monitoring for symptoms of heart failure.

Conclusion

The improvement in insulin sensitivity, which was more evident in the rosiglitazone-treated group than in those treated with diet alone, appeared to be poorly relevant to the cardiac morphometric measurements of obese subjects. Also, if this drug presents some interest, particularly in reducing metabolic risk factors for cardiovascular events, the increase in overload must be considered in the use of rosiglitazone in patients who present underestimated risk factors, such as specific ventricular dysfunction. Probably because of fluid retention, this effect can explain the changes in echocardiographic parameters registered.

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