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Research Article

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Comparison of the Effects of Metformin and Rosiglitazone on Oxidative Stress, Metabolic Parameters, and Anthropometric Measurements in Patients with Type 2 Diabetes Mellitus

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Abstract Aim: In the treatment of type 2 diabetes mellitus (DM), biguanide (metformin) and thiazolidinedione group (rosiglitazone) drugs are used as insulin sensitizers. The aim of this study was to compare the effects of metformin and rosiglitazone on oxidative stress, metabolic parameters and anthropometric measurements in newly diagnosed type 2 DM patients.

Materials and Methods: Forty three type 2 DM patients under 70 years of age were included in the study. Patients were randomized into two drug groups. Seventeen patients in the metformin group and 12 patients in the rosiglitazone group completed the study. In the beginning, third and sixth months of the study, the metabolic and laboratory parameters of the patients were measured and their anthropometric measurements were recorded. Oxidative stress parameters were measured at the beginning and sixth month of treatment.

Results: When metformin and rosiglitazone baseline, third and sixth month anthropometric measurement values were compared, they were found similar. When the metabolic parameters of the basal, third and sixth months of patients receiving metformin and rosiglitazone were compared, insulin and insulin resistance were significantly decreased in favour of rosiglitazone. At the end of the sixth month, there was a significant difference in serum sulfhydryl levels in favour of rosiglitazone.

Conclusion: Metformin and rosiglitazone have similar effects on anthropometric measurements in type 2 DM. The positive effect of rosiglitazone on metabolic parameters and oxidative stress is more pronounced compared to metformin.

Keywords Diabetes Mellitus, metformin, rosiglitazone, oxidative stress

Introduction

Type 2 diabetes mellitus (DM) is the best example of hyperglycaemia resulting from impaired interaction between both insulin sensitivity and pancreatic beta cell function. DM is a chronic and progressive disease that progresses with accelerated atherosclerosis [1]. Peripheral insulin resistance in the pathophysiology of type 2 DM is seen as the most important cause of development of diabetic atherosclerotic complications as well as the formation of metabolic

syndrome [2]. Reducing insulin resistance is seen as the treatment method to be used widely in the treatment of type 2 DM. Impaired insulin secretion or insulin resistance is the underlying cause of type 2 DM development [3].

Insulin sensitizers and drugs to reduce insulin resistance are in two groups as biguanides and thiazolidinediones (TZD). Although biguanides are conventionally considered to be "insulin sensitizers", they act by suppressing hepatic glucose production at the liver level. TZDs are more effective at decreasing insulin resistance at the level of adipose tissue. Metformin inhibits increased gluconeogenesis in type 2 DM and suppresses lipid and cholesterol biosynthesis by transient inhibition of mitochondrial respiratory chain 1. Metformin also reduces intestinal glucose absorption, increases insulin sensitivity, and partially suppresses appetite [4]. TZDs are synthetic molecules that bind to the peroxisome proliferator activated receptor gamma (PPAR-γ) expressed in the adipose tissue, and which activate its effects by activating the transcription of genes affecting adipogenesis, adipocyte differentiation, glucose and lipid metabolism. The effect of TZDs is not the result of a single tissue or system, but different tissues and their effects on each other. Rosiglitazone (RGZ) in the TZD group reduces glucose levels and glucose production and increases glucose clearance. By correcting insulin sensitivity and pancreatic β cell function, it is an option in the treatment of type 2 DM [5].

In this study, in newly diagnosed type 2 DM patients with metformin and rosiglitazone, which are effective on insulin resistance, the effects of metabolic control, oxidative stress and anthropometric measurements were compared.

Materials and Methods

Study Design

This study was conducted between November 2004 and September 2005 in Afyon Kocatepe University Faculty of Medicine Department of Internal Medicine. The study was planned as open-ended, randomized, prospective, single-centre and multidisciplinary. Before the study, approval was obtained from Afyon Kocatepe University Medical Faculty Medical Ethics Committee. Preliminary information was given to the participants and informed consent with signed was obtained from the patients included in the study. During the research, The World Health Organization Declaration of Helsinki and the World Psychiatric Association, Good Clinical Practice and Good Laboratory Practice Rules were complied with.

Study Environment

Forty three type 2 DM patients under the age of 70 who were newly diagnosed were included in the study. Patients with renal failure, liver disease (serum AST or ALT levels over 5 times normal), active infection, history of lactic acidosis, congestive heart failure, coronary artery disease and malignancy were excluded from the study. Before the initiation of medication, a calorie calculated diet program to every patient by an expert dietician was given to reach normal body weight. Of the patients included in the study, 22 to the metformin group and 21 to the rosiglitazone group were randomized. During the treatment, drug doses were gradually increased to the maximum doses (2 grams per day for metformin, 8 milligrams per day for rosiglitazone) that patients could tolerate. One of the patients in the metformin group failed to complete the study due to discontinuation of treatment because of drug-related gastrointestinal complaints, and 4 patients could not complete the study because they did not arrive at their control visits. Nine of the patients in the rosiglitazone group did not arrive at their control visits and were excluded from the analysis. In conclusion, 17 patients (mean age 53 ± 11 years, 10 males) in the metformin group and 12 patients in the rosiglitazone group (mean age 53 ± 7 years, 6 males) completed the study.

Anthropometric Measurements

The height, body weight, waist circumference, hip circumference and thigh circles of all patients were measured at the beginning of the study and at the third and sixth month follow-up visits. Weight measurement was done with a classical scale. Waist circumference, hip circumference, the circumference of the thigh and height were measured with a non-elastic tape measure while the patients were standing upright. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of their height in meters. Waist circumference was measured

from the narrowest diameter of the arcus costarum to the prosessus spina iliaca anterior superior and the hip circumference was measured from the most prominent site of the gluteus maximus at the back and from the largest at the front through the symphysis pubis. The waist-hip ratio was calculated as waist measurement divided by the hip measurement. The circumference of the thigh was measured with a tape measure over 15 cm of the patella.

Laboratory Parameters

At the beginning of the study, fasting blood glucose, insulin, haemoglobin A1c (HbA1c) and fructosamine were studied from the blood samples taken in the morning after 12 hours fasting in the control visits at the third and sixth months. HbA1c levels were measured by high-performance liquid chromatography method using The ADAMS A1c, HA-8180 (ARKRAY, Inc., Kyoto, Japan). Plasma fasting insulin levels were measured by electrochemiluminescence immunoassay method (ECLIA) using the immunoassay analyser (E170, Roche, Hitachi Co., Osaka, Japan). Serums for sulfhydryl (SH) and malonyldialdehyde (MDA) levels were separated and transferred to Eppendorf tubes and stored at -20 ºC. Total SH groups were measured using Ellman's reagent (5,5'-dithiobis–2-nitrobenzoic acid). MDA, the final product of lipid peroxidation, was measured spectrophotometrically by Shimadzu UV-1601 spectrophotometer with thiobarbituric acid (TBA) method. Insulin resistance (HOMA-IR index) was calculated using fasting plasma glucose (mmol / l) X fasting serum insulin (mU / I) / 22.5 formula.

Statistical Analysis

For statistical analysis, SPSS (Statistical Package for the Social Sciences ver. 16.0, SPSS Inc, Chicago, Illinois, USA) computer program was used. Numerical variables were expressed as mean ± standard deviation. In a comparison of independent group means, independent samples t-test (Student t-test) was used. Categorical variables were compared with the Chi-square test. In all statistical analyses, $p < 0.05$ was considered statistically significant.

Results

Demographic characteristics and comparison of the groups are shown in Table 1. The groups were similar in terms of age, gender, hypertension, hyperlipidaemia, obesity and smoking habit. There was no difference between the anthropometric measurements of baseline, third and sixth months of patients receiving metformin and rosiglitazone (Table 2). When the changes in the anthropometric measurements of the third and sixth months of the two groups were compared, there was no difference again (Table 3).

When metformin and rosiglitazone patients were compared with basal, third and sixth month metabolic parameters, fasting blood glucose, fasting blood glucose, HbA1c and fructosamine levels were not different and from the third month onwards, insulin and insulin resistance were significantly lower in the rosiglitazone group (Table 4). The comparison of oxidative stress parameters in baseline and sixth month in patients receiving metformin and rosiglitazone is shown in table 5. While SH levels decreased in sixth month in the metformin group, it increased in rosiglitazone group and at the end of the sixth month, there was a statistically significant difference between the two groups in terms of SH ($p = 0,03$) (Figure 1). At the MDA level, there was a significant decrease in the rosiglitazone group, but there was no significant difference between the two groups at the end of the sixth month ($p = 0.45$).

Table 1: Main characteristics of groups

	Metformin (n=17)	**Rosiglitazone (n=12)**	**p value**
Age (years)	53±11 (35-68)	53±7 (38-65)	0.99
Male (n, %)	10 (59)	6 (50)	0.64
Hypertension (n, %)	5 (33)	3 (24)	0.79
Duration of hypertension (years)	6.6±5.5	6.0±3.6	0.86
Hyperlipidaemia (n, %)	10 (59)	6 (50)	0.64
Duration of hyperlipidaemia (years)	3.1±2.9	1.8±2.0	0.36
Obesity (n, %)	11 (65)	7 (58)	0.73
Smoking (n, %)	4 (24)	2 (17)	0.65

Data were expressed as mean ± standard deviation or n (%).

Table 2: Comparison of the anthropometric measurements of the basal, third and sixth month groups

	Basal			3rd Month			6th Month		
	Metformin	**Rosiglitazone**	**p**	**Metformin**	**Rosiglitazone**	**p**	**Metformin**	**Rosiglitazone**	**p**
Body weight (kg)	82±10	77±10	0.17	81±9	76±12	0.18	80±9	75±12	0.24
BMI (kg / m^2)	30.5±3.3	29.6±4.1	0.53	30.2±3.1	28.7±4.3	0.30	29.5±2.9	28.3±4.3	0.37
Waist circumference (cm)	108±10	101±6	0.07	107±10	99±7	0.06	105±9	99±5	0.07
Hip circumference (cm)	109±9	103±8	0.12	108±9	103±9	0.19	108±8	102±9	0.14
Waist-to-hip ratio	0.99±0.07	0.98±0.08	0.75	0.99±0.07	0.96±0.06	0.29	0.98±0.07	0.88±0.31	0.32
Thigh circumference (cm)	49±4	47±5	0.20	50±4	47±5	0.17	49±4	46±5	0.11

Data were expressed as mean ± standard deviation.

Table 3: Comparison of third and sixth month change values of anthropometric measurements

	3rd month - basal change			6th month - basal change		
	Metformin	**Rosiglitazone**	**p**	**Metformin**	**Rosiglitazone**	**p**
Body weight (kg)	-0.65±1.41	-1.70±1.83	0.11	-2.53±2.27	-2.80±2.57	0.78
BMI (kg / m^2)	-0.23±0.51	-0.68±0.75	0.08	-0.92±0.80	-1.12±1.06	0.58
Waist circumference (cm)	-0.59±1.33	-2.00±4.03	0.19	-1.88±2.00	-2.11±7.56	0.93
Hip circumference (cm)	-0.35±1.22	-0.80±1.48	0.40	-0.71±1.26	-1.70±1.83	0.11
Waist-to-hip ratio	0.00±0.01	-0.01±0.03	0.34	-0.01±0.02	-0.10±0.29	0.38
Thigh circumference (cm)	-0.24±1.52	-0.10±1.79	0.84	-0.41±1.66	-0.80±2.49	0.63

Data were expressed as mean ± standard deviation.

Table 4: Comparison of metabolic parameters of the basal, third and sixth month groups

	Basal			3rd Month			6th Month		
	Metformin	**Rosiglitazone**	**p**	**Metformin**	**Rosiglitazone**	**p**	**Metformin**	**Rosiglitazone**	**p**
Fasting glucose (mg / dl)	193±94	180±54	0.64	144±43	144±36	0.99	131±25	137±50	0.66
Postprandial glucose (mg / dl)	249±77	235±72	0.41	190±40	208±76	0.44	171±38	177±72	0.73
Haemoglobin A1c (%)	7.8±2.8	6.7±2.3	0.21	6.4±2.4	6.1±1.2	0.64	6.1±2.1	5.7±1.2	0.54
Fructosamine (µmol / L)	368±121	352±91	0.68	302±87	306±84	0.91	253±71	301±112	0.12
Insulin (mU / l)	15.3±4.1	13.3±9.6	0.34	13.0±4.0	9.8±4.1	0.03	10.4±3.5	6.0±2.2	<0.001
Insulin resistance	6.98±3.75	5.5±4.06	0.33	4.39±1.29	3.28±1.38	0.04	3.39±1.05	1.88±0.84	<0.001

Data were expressed as mean ± standard deviation.

Table 5: Comparison of the basal and sixth month oxidative stress parameters of the groups

	Basal			6th Month		
	Metformin	**Rosiglitazone**	**p**	**Metformin**	**Rosiglitazone**	**p**
SH (nmol/ml)	548±181	567±211	0.78	509±176	662±203	0.03
MDA (umol/l)	1.27±0.30	1.30±0.33	0.83	1.23±0.45	1.09±0.45	0.45

SH: Sulfhydryl, MDA: Malonyldialdehyde

Data were expressed as mean ± standard deviation.

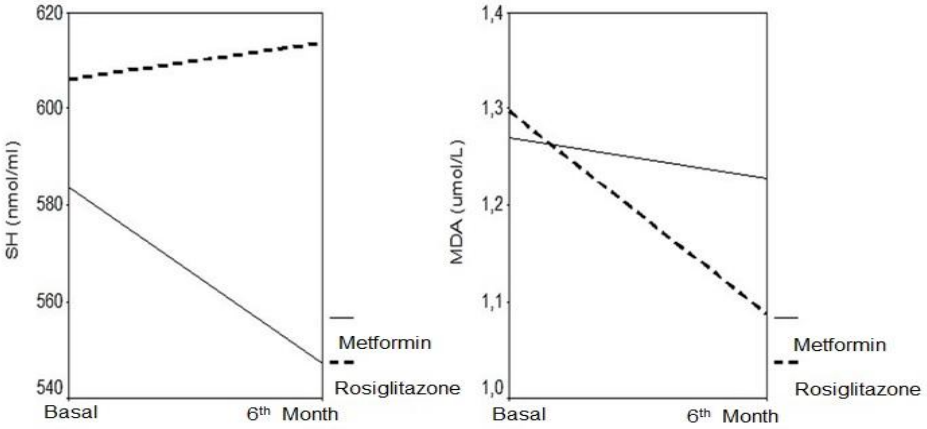

Figure 1: Sulfhydryl (SH) and malonyldialdehyde (MDA) levels of groups by months

Discussion

Metformin is a well-known oral antidiabetic drug for the treatment of type 2 DM, it has been shown to improve the lipoprotein profile, cause no increase in body weight and cause a decrease in body weight in obese diabetics [6]. Rosiglitazone is a drug of the TZD group and a PPAR-γ receptor agonist. Rosiglitazone reduces insulin resistance, plasma glucose and HbA1c. It also improves lipid profile and endothelial function in a positive way by reducing free toxic radicals and improving fatty liver [7].

The relationship between oxidative stress and cardiac diseases such as myocardial infarction and rheumatic diseases such as rheumatoid arthritis, many diseases including cancer, neurological diseases, asthma, DM, and aging were shown [8]. Oxidative stress plays an important role in the pathogenesis of DM and the late complications of DM. Non-enzymatic glycation, auto-oxidative glycation, sorbitol activity, various changes in antioxidant defence system, causes such as hypoxia are mechanisms that increase oxidative stress in DM [9]. Hyperglycaemia is accompanied by an accelerated formation of advanced glycation end products. In addition to cytotoxicity in the neuronal cell of end-products of advanced glycation, it has been shown to cause oxidative stress and inflammatory reactions [10]. It is emphasized by researchers that prolonged oxidative stress and changes in antioxidant capacity may be related to the emergence of chronic complications of DM [11].

Protein SH groups are important antioxidants that have the ability to break the oxidation chain. Plasma protein SH groups are susceptible to oxidative damage and have been shown to decrease in the cases of oxidative damage such as coronary artery disease, rheumatoid arthritis and DM [12]. In this study, MDA and antioxidant parameters were studied from the oxidative stress parameters. When SH levels were compared in the sixth month, it was seen that the SH level decreased in the metformin group and increased in the rosiglitazone group. MDA levels were decreased in both drug groups, more prominent in the rosiglitazone group. In the study conducted by Yılmaz et al., in patients with polycystic ovary syndrome, the given level of rosiglitazone increased the total antioxidant status level and decreased the MDA level. There was no change in the metformin group [13]. In another study by Atamer et al., rosiglitazone was found to provide better blood glucose regulation in uncontrolled type 2 DM patients and had a positive effect on antiatherogenic paraoxonase activity. In type 2 DM patients, rosiglitazone decreases homocysteine and MDA levels and increases serum paraoxonase 1, apolipoprotein A1 and high-density lipoproteincholesterol

levels (HDL) cholesterol levels [14]. In this study, a more significant decrease in MDA level was observed in the group receiving rosiglitazone. It is thought that the decrease in MDA levels can be explained by the fact that it is not statistically significant at the end of the sixth month and the duration of the study is limited to 6 months and by the low number of patients.

The increase in SH levels of rosiglitazone may probably be due to its effect on increasing antioxidant enzyme activity [15]. No studies have been published investigating the effects of rosiglitazone on SH levels in DM patients. In some studies, it was observed that rosiglitazone had antioxidant properties by decreasing nicotinamide adenine dinucleotide (NADH) dependent superoxide production. Kim and et al. reported that rosiglitazone had a protective effect on cardiomyocytes under oxidative stress through the thioredoxin system [16]. In a study on mice conducted by Calkin and et al., an increase in nicotinamide adenine dinucleotide phosphate (NADPH) dependent superoxide production in aortic tissues was shown in DM in comparison with the control group mice [17]. Antioxidant activity of rosiglitazone showed by this mechanism was also shown in human endothelial cells, hypercholesterolemic rabbits and obese individuals [18]. In DM, free oxygen radicals increase. However, with the increase in the reactive oxygen species (ROS) level in hyperglycemia, oxidative stress is further increased. Oxidative stress studies are important in preventable diseases such as DM by lifestyle and medical treatment.

In conclusion, in this study, compared to metformin, the effects of rosiglitazone on insulin and insulin resistance were further reduced and the positive effects of rosiglitazone on oxidative stress were demonstrated. The positive effect of a drug used in the medical treatment of DM on oxidative stress mechanisms suggests that DM will lead to a decrease in the development of chronic complications. Rosiglitazone stands out in this respect.

Conclusion

Metformin and rosiglitazone cause a decrease in body weight and BMI in patients with type 2 DM. The effects of both drugs on anthropometric measurement values are similar. Compared to metformin, the positive effect of rosiglitazone on metabolic parameters and oxidative stress is more significant.

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