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Effects of rosiglitazone treatment on insulin resistance and TNF-alpha levels in patients with chronic kidney disease: a prospective study

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Abstract. – AIM: The aim of the study was to investigate the effects of rosiglitazone treatment on insulin resistance (IR) and tumor necrosis factor-alpha (TNF-alpha) levels in non-diabetic chronic kidney disease (CKD) patients with IR.

PATIENTS AND METHODS: Thirty non-diabetic CKD patients with IR were enrolled in the study. Patients were grouped into two: group 1 (n = 15) received rosiglitazone 4 mg tablet for 3 months and patients who did not receive rosiglitazone treatment constituted the group 2 (n = 15). Baseline and after rosiglitazone treatment, homeostatis model assessment-insulin resistance (HOMA-IR) and TNF-alpha levels were measured.

RESULTS: There were no statistical differences in gender, age, HOMA-IR and TNF-alpha levels among group 1 and group 2 ($p > 0.05$ for all). Compared to baseline in group 1, significant differences were found in HOMA-IR and TNF-alpha levels after 3 months ($p = 0.023$; $p = 0.001$, respectively).

CONCLUSIONS: Our study indicates that, rosiglitazone treatment improves the IR and decreases TNF-alpha levels in non-diabetic patients CKD with IR.

Key Words:
Rosiglitazone, Insulin resistance, Chronic kidney disease, TNF-alpha.

Introduction

Chronic kidney disease (CKD) is a chronic microinflammatory process of cytokine dysregulation and increased insulin resistance (IR) is a known concept in these patients. Tumor necrosis factor-alpha (TNF-alpha) is a proinflammatory cytokine and has been shown to increase in chronic renal failure patients in some studies[1-6]. The association between insulin resistance and TNF-alpha has been reported in both diabetic and nondiabetic patients[7-9]. Thiazolidinediones may exert some beneficial effects on the kidney, although the exact mechanism is not well understood. The main protective mechanisms at kidney level include haemodynamic, anti-inflammatory, antiproliferative and other metabolic effects[10].

Although based upon this relationship between IR, TNF-alpha and thiazolidinediones mentioned above, no clinical research has been performed yet to confirm this issue. By this way, we aimed in our study to investigate whether the rosiglitazone treatment improves IR or decreases TNF-alpha levels in non-diabetic CKD patients with IR.

Patients and Methods

Study Design and Patients

This prospective cohort study was conducted at the Unit of Nephrology of Sisli Etfal Education and Research Hospital, Istanbul, Turkey. Prior to subject recruitment, the study protocol was reviewed and approved by the local Ethics Committee, in accordance with the ethical principles for human investigations, and written informed consents were obtained from all the patients. Between June-2008 to January-2009 consecutively 30 age-gender-matched CKD patients with IR were recruited to the study.

Patients with CKD were grouped into two: group 1 (n =15) received rosiglitazone 4 mg tablet for 3 months and patients who did not receive rosiglitazone treatment constituted the group 2 (n = 15). Baseline and after rosiglitazone treatment, metabolic parameters, IR and TNF-alpha levels were measured. All of the patients were receiving antihypertensive drugs, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium

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channel blockers and alpha receptor blockers. Additional antihypertensive agents were added for patients as needed. Exclusion criteria were as follows: patients who were receiving antidiabetic agents, fasting blood glucose levels above 126 mg/dL, HOMA-IR levels < 2.34, glomerular filtration rates < 15 ml/min, secondary hypertension, severe systemic diseases (chronic liver diseases, malignancies, etc.), recent acute illness and/or history of any overt chronic inflammatory disease.

Baseline Definitions and Measurements

The diagnosis of diabetes mellitus (DM) was based on the American Diabetes Association 2010 criteria and on a previous history of diabetes (anti-diabetic medications usage)[11]. Height and weight were measured according to standardized protocols. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2). Blood pressure was measured using a mechanical sphygmomanometer in the medical office setting. In each subject, after 15 minutes of comfortably sitting, the average of three blood pressure measurements was calculated. IR was assessed using the homeostasis model assessment (HOMA-IR) originally described by Matthews et al[12]. HOMA-IR was calculated using the following formula: HOMA-IR (mmol/L x μU/ml) = fasting glucose (mmol/L) x fasting insulin (μU/ml)/22.5. No universal HOMA-IR cut-off value has been established for IR. In the present study, a HOMA-IR value greater than 2.34 was accepted as the indicator for IR in Turkish population[13].

Biochemical Analysis

All blood samples were collected from an antecubital vein with the patient in the supine position after a 12 hour overnight fast. Fasting plasma glucose, total cholesterol, triglyceride, LDL cholesterol levels were measured by enzymatic colorimetric system (Diagnostic Products Corp. Los Angeles, CA, USA), serum creatinine levels by kinetic colorimetric system (Diagnostic Products Corp. Los Angeles, CA, USA), insulin levels by electrochemiluminescence immunometric assay (Roche Diagnostics GMBH Mannheim, Germany) HbA1c by high performance liquid chromatography assay (Primus Diagnostics, Kansas City, MO, USA) and TNF-alpha by electrochemiluminescence assay (Anogen, Mississauga, Ontario, Canada). High sensitivity C-reactive protein (hs-CRP) levels were measured by nephelometric method and by using Beckman Coulter Immage kit (Beckman Coulter Ireland Inc, Mervue, Galway, Ireland).

Renal function was defined according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) definitions. CKD is defined according to the presence or absence of kidney damage and level of kidney function. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. Among individuals with CKD, the stage is defined by the level of glomerular filtration rate (GFR) (stage 1-5)[14].

Statistical Analysis

All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov tests were used to test the normality of data distribution. The data were expressed as arithmetic means and standard deviations. The chi-square test was used to compare the categorical variables between groups. Independent sample *t*-test and Mann-Whitney U tests were respectively used in normally and non-normally distributed continuous variables between groups. Paired *t*-test and Wilcoxon signed-rank tests were used to analyze changes within each group. Two-sided p value < 0.05 was considered statistically significant.

Results

Baseline clinical, laboratory and demografic characteristics of patients were presented on Table I. There were no statistical differences in gender, age, body mass index (BMI), eGFR, hs-C reactive protein (CRP), HOMA-IR and TNF-alpha levels among group 1 and group 2 ($p > 0.05$ for all) (Table I). In group 1; systolic blood pressure, diastolic blood pressure, fasting blood glucose, fasting insulin level, hs-CRP, HOMA-IR and TNF-alpha levels were significantly decreased after 3 months ($p = 0.006$, $p = 0.002$, $p = 0.048$, $p = 0.038$, $p = 0.005$, $p = 0.023$, $p = 0.001$, respectively), whereas there were no statistical difference in serum creatinine, HbA1c, total cholesterol, triglyceride, LDL and HDL levels ($p > 0.05$, for all) (Table II). Compared to baseline parameters in group 2, there were no statistical difference found in all clinical and laboratory features after 3 months (Table III).

Table I. Baseline comparison of the demographic, clinical and laboratory characteristics.

	Group 1 (n = 15)	Group 2 (n = 15)	p
Gender, male/female	6/9	9/6	NS[a]
Age, years	54.86 ± 9.43	52.06 ± 17.81	NS[b]
BMI, kg/m^2	25.82 ± 3.77	23.49 ± 2.25	NS[b]
Systolic BP, mmHg	162.00 ± 12.64	158.66 ± 16.42	NS[b]
Diastolic BP, mmHg	90.66 ± 7.98	88.00 ± 9.41	NS[b]
FBG, mg/dL	93.40 ± 11.50	97.33 ± 9.37	NS[b]
Urea, mg/dL	87.66 ± 58.15	76.06 ± 27.20	NS[b]
Creatinine, mg/dL	2.03 ± 0.93	2.33 ± 0.76	NS[b]
Total cholesterol, mg/dL	214.80 ± 49.20	198.07 ± 40.70	NS[b]
Triglyceride, mg/dL	152.13 ± 55.90	124.07 ± 61.36	NS[b]
LDL, mg/dL	134.86 ± 45.60	127.00 ± 41.81	NS[b]
HDL, mg/dL	49.40 ± 10.56	46.00 ± 7.03	NS[b]
Fasting insulin, μU/mL	14.80 ± 11.40	16.07 ± 8.53	NS[c]
HbA1c, %	5.15 ± 0.39	5.11 ± 0.62	NS[b]
eGFR, mL/min	46.45 ±2 6.90	37.64 ± 22.25	NS[b]
HOMA-IR	3.51 ± 1.12	3.92 ± 1.33	NS[b]
TNF-α, pg/mL	54.1 ± 37.4	61.2 ± 47.06	NS[b]
Hs-CRP, mg/L	15.64 ± 24.71	6.99 ± 8.61	NS[c]

All measurable values were given with mean ± standard deviation. NS: non significant, HbA1c: glycosylated haemoglobin, BP: blood pressure, BMI: body mass index, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, HDL: high density lipoprotein, HOMA-IR: homeostasis model of assessment-insulin resistance, TNF: tumor necrosis factor, Hs-CRP: high sensitivity C-reactive protein Chi-square[a], Independent sample *t* test[b] and Mann-Whitney U[c] tests were used.

Discussion

To the best of our knowledge, this is the first report to investigate the effect of roziglitazone treatment on IR and TNF-alpha levels in non-diabetic CKD patients with IR. The main findings of this study were that, (1) rosiglitazone treatment improves IR and (2) decreases TNF-alpha levels in non-diabetic CKD patients with IR.

Although HOMA-IR is an inexpensive and simple tool used extensively for the determination of IR in large-scale studies, a threshold value

Table II. Comparison of laboratory and clinical characteristics in group 1 after 3 months.

	Before treatment (n = 15)	After treatment(n = 15)	p
BMI, kg/m^2	25.82 ± 3.77	24.85 ± 3.89	NS[a]
Systolic BP, mmHg	166.66 ± 13.22	143.33 ± 18.02	0.006[a]
Diastolic BP, mmHg	94.44 ± 5.27	82.22 ± 8.33	0.002[a]
FBG, mg/dL	93.40 ± 11.50	87.7 ± 9.30	0.048[a]
Creatinine, mg/dL	2.03 ± 0.93	1.96 ± 1.03	NS[a]
Total cholesterol, mg/dL	214.80 ± 49.20	202.50 ± 49.20	NS[a]
Triglyceride, mg/dL	152.13 ± 55.90	146.13 ± 53.38	NS[a]
LDL, mg/dL	134.86 ± 45.60	127.58 ± 45.82	NS[a]
HDL, mg/dL	49.40 ± 10.56	51.00 ± 10.88	NS[a]
Fasting insulin, μU/mL	14.80 ± 11.40	9.64 ± 3.37	0.038[b]
HbA1c, %	5.15 ± 0.39	5.03 ± 0.24	NS[a]
eGFR, mL/min	46.45 ± 26.90	49.35 ± 29.50	NS[a]
HOMA-IR	3.51 ± 1.12	2.10 ± 0.78	0.023[a]
TNF-alpha, pg/mL	54.10 ± 37.40	35.20 ± 29.00	0.001[a]
Hs-CRP, mg/L	15.64 ± 24.71	10.28 ± 22.50	0.005[b]

All measurable values were given with mean ± standard deviation. NS: non significant, HbA1c: glycosylated haemoglobin, BP: blood pressure, BMI: body mass index, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, HDL: high density lipoprotein, HOMA-IR: homeostasis model of assessment-insulin resistance, TNF: tumor necrosis factor, Hs-CRP: high sensitivity C-reactive protein. Paired sample *t* test[a] and Wilcoxon signed-rank[b] tests were used.

Table III. Comparison of laboratory and clinical characteristics in group 2 after 3 months.

	Before treatment (n = 15)	After treatment (n = 15)	p
BMI, kg/m^2	23.49 ± 2.25	23.10 ± 2.15	NS[a]
Systolic BP, mmHg	158.66 ± 16.42	141.33 ± 16.84	NS[a]
Diastolic BP, mmHg	88.00 ± 9.41	76.66 ± 12.34	NS[a]
FBG, mg/dL	97.33 ± 9.37	93.80 ± 12.09	NS[a]
Creatinine, mg/dL	2.33 ± 0.76	2.46 ± 0.96	NS[a]
Total cholesterol, mg/dL	198.07 ± 40.70	191.00 ± 39.30	NS[a]
Triglyceride, mg/dL	124.07 ± 61.36	134.67 ± 59.80	NS[a]
LDL, mg/dL	127.00 ± 41.81	121.68 ± 35.65	NS[a]
HDL, mg/dL	46.00 ± 7.03	43.90 ± 8.98	NS[a]
Fasting insulin, µU/mL	16.07 ± 8.53	15.85 ± 8.67	NS[b]
HbA1c, %	5.11 ± 0.62	5.02 ± 0.41	NS[a]
eGFR, mL/min	37.64 ± 22.25	36.40 ± 23.02	NS[a]
HOMA-IR	3.92 ± 1.33	3.73 ± 1.16	NS[a]
TNF-alpha, pg/mL	61.2 ± 47.06	60.20 ± 35.80	NS[a]
Hs-CRP, mg/L	6.99 ± 8.61	7.71 ± 9.26	NS[b]

All measurable values were given with mean ± standard deviation. NS: non significant, HbA1c: glycosylated haemoglobin, BP: blood pressure, BMI: body mass index, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, LDL: low density lipoprotein, HDL: high density lipoprotein, HOMA-IR: homeostasis model of assessment-insulin resistance, TNF: tumor necrosis factor, Hs-CRP: high sensitivity C-reactive protein. Paired sample *t* test[a] and Wilcoxon signed-rank[b] tests were used.

for IR has not yet been standardized[5]. Thus, different HOMA-IR levels used to define IR may result in variability of waist circumference cut-off values to predict insulin resistance. For instance, in a retrospective study on 2746 healthy subjects, Wahrenberg et al[16] defined a HOMA-IR value > 3.99 as insulin resistance and reported the waist circumference limit that best predicted IR as 100 cm for both men and women. Other studies have led to different estimates: Bonora et al[17] reported a HOMA-IR value of 2.77 for IR among non-obese individuals without metabolic disorder, and Ascaso et al[18] used a cut-off value of 2.6 for subjects with normal glucose tolerance. These different HOMA-IR cut-off values for IR in different studies may reflect varying characteristics of study populations, suggesting the need for defining population-specific HOMA-IR cut-off values for the prediction of IR. In the present study, we used HOMA-IR > 2.34 as IR, which was accepted value of the IR prediction in Turkish population.

Increased IR is a known phenomen and has been shown by several studies in non-diabetic patients with CKD[19-20]. Prevalence of inflammation is high in CKD patients, as reflected by the elevated levels of acute phase reactants such as serum CRP and several proinflammatory cytokines, whereas systemic inflammation is an important potential factor in the pathogenesis of IR in patients with CKD[21-23]. TNF-alpha is an inflammatory cytokine and has been shown to increase IR, whereas its neutralization with thiazolidinediones has been shown to improve insulin sensitivity in some studies[24-25]. Besides, Demirbas et al[26] showed that, hypertensive patients have IR and higher TNF-alpha levels, but they did not find any correlation between TNF-alpha levels and insulin resistance in non-diabetic patients with hypertension.

Thiazolidinediones are insulin sensitisers which reduce insulin resistance, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. These antidiabetic oral agents are interesting in the clinical management of patients with type-2 diabetes and end stage renal disease due to the fact that they are primarily metabolised at hepatic level, and, therefore, they do not accumulate in CKD[27]. These drugs may exert some beneficial effects on the kidney, although the exact mechanism is not well understood. The main protective mechanisms on kidney level include haemodynamic, antiproliferative, and other metabolic effects. Another important mechanism of renal protection by PPAR-γ agonists is related to the inflammatory process. PPAR-γ stimulation inhibits inflammatory cytokine production by macrophages[28]. Rosiglitazone is one of the thiazolidinediones and its treatment has been shown to improve insulin resistance, decrease inflammatory markers such as fibrinogen and CRP in non-diabetic subjects with metabolic syndrome[29-30]. In our study, rosiglitazone treatment significantly improved IR

and decreased inflammatory markers such as hs-CRP and TNF-alpha levels after 3 months in non-diabetic patients with CKD.

TNF-alpha and hs-CRP levels have been shown to be an independent risk factors for hypertension in several studies, however these remains unclear. Also, IR contributes and precipitates the progression of hypertension[31-34]. However, prospective and randomized studies with antihypertensive drugs have demonstrated differences between different classes of drugs regarding effects on insulin sensitivity. Thus, treatment with beta-blockers or diuretics is associated with impaired insulin sensitivity, whereas most modern calcium channel blockers are neutral. The inhibition of the renin-angiotensin system (RAS) with either angiotensin converting enzyme inhibitors (ACEIs) or AT1 angiotensin receptor blockers (ARBs) consistently and significantly reduces the incidence of type 2 diabetes. The mechanisms underlying this protective effect appear to be complex and may involve an improvement of both insulin sensitivity and insulin secretion[35,36]. In addition to main findings of the present study, rosiglitazone treatment significantly decreased systolic and diastolic blood pressures after 3 months. Although not definitive, this may be developed as a result of improving IR, decreasing TNF-alpha and hs-CRP levels by rosiglitazone treatment. There were no changes in hypertensive drugs used by patients during the study, but only 3 patients (1 patient in group 1, 2 patients in group 2) were added calcium channel blocker as nifedipine

Certain limitations of the present study should be considered. First of all, sample size was relatively small. Although the IR was accepted as > 2.34 in our study, HOMA-IR value needs a great number of patients.

In conclusions, our study indicates that rosiglitazone treatment improves IR and decreases inflammatory markers in non-diabetic patients with CKD. Therefore, future large prospective cohort studies are needed to clarify this issue.

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