ORIGINAL ARTICLE

# Rosiglitazone treatment in nondiabetic subjects with nonalcoholic fatty liver disease

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**KEY WORDS**

adiponectin, fatty liver disease, glucose intolerance, insulin resistance, rosiglitazone

**ABSTRACT**

**INTRODUCTION** Pharmacological treatment options for nonalcoholic fatty liver disease (NAFLD) are limited. It has been suggested that thiazolidinediones may be useful in NAFLD treatment.

**OBJECTIVES** An open-label prospective study was conducted to assess the efficacy and safety of rosiglitazone treatment in nondiabetic subjects with NAFLD.

**PATIENTS AND METHODS** A total of 27 subjects (mean age 44 ±11 years, body mass index 29.2 ±3.1 kg/m$^2$), with biopsy-confirmed NAFLD and no other complaints, were treated with rosiglitazone 4 mg daily for 6 months.

**RESULTS** No adverse events were observed during a 6-month treatment with rosiglitazone. Liver enzymes gradually decreased (alanine transaminase from 101 ±59 to 58 ±39 IU/l, aspartate transaminase from 52 ±24 to 37 ±15 IU/l; $P$ <0.001). Plasma insulin levels decreased significantly by 30% to 50% in each time point of the oral glucose tolerance test. The homeostatic model assessment index decreased from 3.73 ±1.89 to 2.06 ±1.68 ($P$ <0.001). No significant changes in plasma glucose were noted. Plasma adiponectin increased from 2198 ±1853 to 5734 ±1999 ng/ml ($P$ <0.001). There were no statistically significant changes in body weight, glycated hemoglobin $A_{1c}$, plasma lipids, or leptin.

**CONCLUSIONS** Rosiglitazone treatment in patients with NAFLD is safe, well-tolerated and leads to a significant improvement in liver function and insulin sensitivity, without adversely affecting the lipid profile.

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**INTRODUCTION** Nonalcoholic fatty liver disease (NAFLD) is becoming the epidemic of the 21st century, similarly to obesity and type 2 diabetes. Its prevalence is estimated at 17% to 44% in the developed countries and has been increasing over the recent decade, partly because a better understanding of its pathogenesis and improved diagnostic procedures allow to identify more cases.[1,2] NAFLD is closely associated with overweight and has been repeatedly suggested to constitute a component of metabolic syndrome (MS).[3] This link is based on the findings that NAFLD subjects show significant insulin resistance, which is closely associated with abdominal obesity.[3,4] Both insulin resistance and abdominal obesity have also been acknowledged as potential causes of MS.[5,6]

The mechanism of insulin resistance observed in subjects with NAFLD has not been fully understood so far. Triglycerides that accumulate in the liver account for the development of hepatic insulin resistance. However, the association between fatty liver and insulin resistance is more complex because there is a two-way relationship between the two conditions.[7] Increased fat content is responsible for resistance of hepatocytes to insulin, and, at the same time, peripheral insulin resistance, through increased lipolysis, leads to enhanced triglyceride influx to the liver.[8] Considering this background, NAFLD, which

is a marker of insulin resistance, becomes an active player itself and leads to the impairment of glucose tolerance. Thus, NAFLD and its more advanced form, nonalcoholic steatohepatitis, have been confirmed as risk factors for glucose intolerance and diabetes. Numerous studies have shown that the risk of developing diabetes in individuals with NAFLD is 2- to 4-fold higher than in subjects with normal liver function.[9,10]

Clinical experience with NAFLD treatment is limited. The standard of care includes nonpharmacological intervention with the aim to achieve weight reduction.[11] Antiobesity agents (sibutramine, orlistat, phentermine) and statins have been shown to reduce fat content in the liver, but no specific treatment for NAFLD has been approved so far. Insulin-sensitizing antidiabetic agents, including metformin or glitazones, have been suggested as a possible therapeutic option.[11-15] We designed an open-label prospective study to assess the efficacy and safety of the modern insulin sensitizer, rosiglitazone, in the treatment of nondiabetic subjects with NAFLD. The available data on the use of rosiglitazone in patients with diabetes and NAFLD suggest that the drug might also additionally improve liver function.[16,17] The present uncontrolled study was conducted in the clinical setting of a regular outpatient clinic to assess the effects of rosiglitazone treatment in nondiabetic NAFLD subjects. While we accept limitations of open-label, uncontrolled studies, the main aim of our investigation was to elucidate the impact of rosiglitazone on liver function and NAFLD-related metabolic disorders.

**PATIENTS AND METHODS** The study included 27 men (mean age 44 ±11 years, body weight 88.4 ±14.7 kg, body mass index [BMI] 29.2 ±3.1 kg/m$^2$, waist circumference 103 ±16 cm) with NAFLD confirmed by elevated activity of alanine aminotransferase (ALT), ultrasound examination, and liver biopsy. Low-to-none alcohol consumption was established on the basis of the patient's self-report. Apart from NAFLD, the patients were healthy, did not report chronic use of any medications, and their medical history was unremarkable. Metabolic syndrome, as defined by the International Diabetes Federation, was not observed in this study group. The subjects had not been treated for glucose intolerance, diabetes, obesity, hypertension or liver diseases, and they did not have cirrhosis in the liver histologic examination. Furthermore, they were negative for viral hepatitis C antibodies and hepatitis B antigen. Thirteen healthy men matched for age and body weight served as baseline controls (mean [± standard deviation] age 45 ±13 years, body weight 90.5 ±15.6 kg, BMI 30.4 ±3.3 kg/m$^2$, waist circumference 101 ±14 cm).

All subjects with NAFLD, after providing written informed consent, started a 6-month unblinded treatment with rosiglitazone 4 mg taken once daily with the morning meal. At baseline and at 2, 4, and 6 months, they had outpatient appointments for body weight assessment, blood sampling, and drug administration. No particular low-calorie diet or lifestyle modification treatment was recommended to the subjects during the study period so as to limit the confounding effect of nonpharmacological treatment.

Plasma ALT and aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), plasma glucose as well as glycated hemoglobin $A_{1c}$ ($HbA_{1c}$) and hematocrit were assessed at each visit. At baseline and at 6 months, the oral prolonged glucose tolerance test (OGTT) was conducted according to the World Health Organization protocol, with blood sampled at 0, 60, 120, 180 and 240 minute for plasma glucose and insulin measurements.

At baseline and at 6 months, fasting plasma total cholesterol, low-density and high-density lipoprotein cholesterol, triglycerides, adiponectin, and leptin were measured. The homeostatic model (HOMA) index[18] was calculated at baseline and at 6 months. Drug tolerance was assessed at each visit. After 6 months rosiglitazone treatment was stopped and 4 weeks later the subjects were assessed for any adverse effects.

In the control group, the OGTT and plasma assays were performed only at baseline.

Statistical analysis included the use of Student *t* test for unpaired data (to assess differences in means between NAFLD and control subjects) and paired data (to assess differences in means of longitudinal data in individuals with NAFLD). Prior to the above test, normal distribution of the data was confirmed with the Kolmogorov-Smirnov and Lilliefors tests. If normal distribution was not confirmed, nonparametric Mann-Whitney test was used. The value of $P < 0.05$ was considered statistically significant.

The study protocol was approved by the Bioethics Committee at the Medical University of Lodz, Łódź, Poland.

**RESULTS** Treatment with rosiglitazone was safe; no adverse events had been observed during the whole study period. Liver function enzymes gradually decreased during the 6 months of treatment (ALT from 101 ±59 to 58 ±39 IU/l, AST from 52 ±24 to 37±15 IU/l; $P < 0.001$; **FIGURE 1**, **TABLE 1**). Insulin levels decreased significantly by 30% to 50% in each time point of the OGTT (**FIGURE 2**). The HOMA index decreased from 3.73 ±1.89 to 2.06 ±1.68 ($P < 0.001$). However, no change in plasma glucose in the OGTT was observed (**FIGURE 2**, **TABLE 2**). Adiponectin increased from 2198 ±1853 to 5734 ±1999 ng/ml ($P < 0.001$). Mean body weight and waist circumference at 6 months did not differ significantly compared with baseline (91.2 ±16.2 kg, $P > 0.05$ and 105 ±17 cm, $P > 0.05$, respectively). There were no statistically significant changes in mean fasting plasma glucose, $HbA_{1c}$, plasma lipids, or leptin. Hematocrit decreased significantly during the first 2 months from 45.5 ±2.7 at baseline to 44.2 ±3.1 ($P < 0.05$)

**TABLE 1** Results of biochemical and hematological assays in the study group and controls

| | NAFLD subjects | | | | Controls |
|---|---|---|---|---|---|
| | baseline | 2 months | 4 months | 6 months | |
| ALT, IU/l | 101 ±59 | 64 ±32[a] | 67 ±45[a] | 58 ±39[a] | 23 ±12[c] |
| AST, IU/l | 52 ±24 | 42 ±19[a] | 42 ±26[a] | 37 ±15[a] | 28 ±8[c] |
| GGT, IU/l | 62 ±16 | – | – | 49 ±13[a] | 43 ±15[d] |
| $HbA_{1c}$, % | 5.84 ±0.74 | 5.87 ±0.78 | 5.43 ±0.31 | 5.62 ±0.52 | 5.6 ±0.27 |
| HOMA | 3.73 ±1.89 | – | – | 2.06 ±1.68[a] | 2.34 ±1.87[d] |
| total cholesterol, mg/dl | 223 ±51 | – | – | 222 ±35 | 196 ±34[c] |
| LDL cholesterol, mg/dl | 137 ±42 | – | – | 139 ±25 | 117 ±34[c] |
| HDL cholesterol, mg/dl | 44 ±9 | – | – | 42 ±8 | 60 ±15[c] |
| triglycerides, mg/dl | 231 ±167 | – | – | 266 ±189 | 102 ±58[e] |
| adiponectin, ng/ml | 2198 ±1853 | – | – | 5734 ±1999[a] | 6681 ±4329[d] |
| leptin, ng/ml | 43.5 ±18.4 | – | – | 38.4 ±12.3 | 63.2 ±16.3 |
| hematocrit,% | 45.5 ±2.7 | 44.2 ±3.1[b] | 44.4 ±3.0[b] | 43.6 ±3.6[b] | 46.2 ±3.1 |

**a** $P < 0.001$ vs. baseline
**b** $P < 0.05$ vs. baseline and controls
**c** $P < 0.05$ vs. all NAFLD group values
**d** $P < 0.05$ vs. baseline NAFLD group values
**e** $P < 0.001$ vs. all NAFLD group values

Abbreviations: ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – γ-glutamyltransferase, $HbA_{1c}$ – glycated hemoglobin $A_{1c}$, HDL – high-density lipoprotein, HOMA – homeostatic model assessment, LDL – low-density lipoprotein, NAFLD – nonalcoholic fatty liver disease

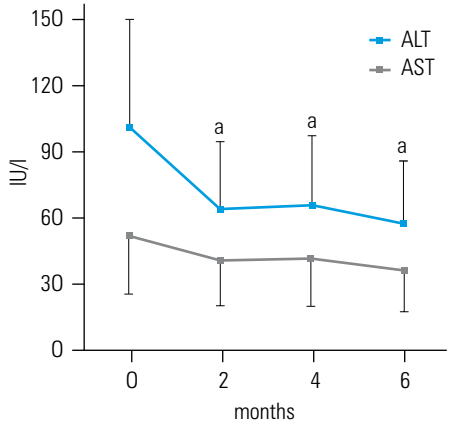


**FIGURE 1** Activity of alanine (ALT) and aspartate (AST) aminotransferases in subjects with nonalcoholic fatty liver disease
**a** $P < 0.001$ vs. baseline values for ALT and AST

and remained stable between the fourth and sixth month (TABLE 1).

**DISCUSSION** Rosiglitazone was introduced as a drug targeting insulin resistance with high pharmacodynamic precision. Given the promising results of the early studies on rosiglitazone, the drug has been recommended by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) as a second-line drug for type 2 diabetes.[19] In 2007, Nissen and Wolski[20] raised suspiscion in their meta-analysis that its use might increase the risk of myocardial infarction in patients with type 2 diabetes.[20] Although this risk was not confirmed in prospective randomized clinical trials[21]

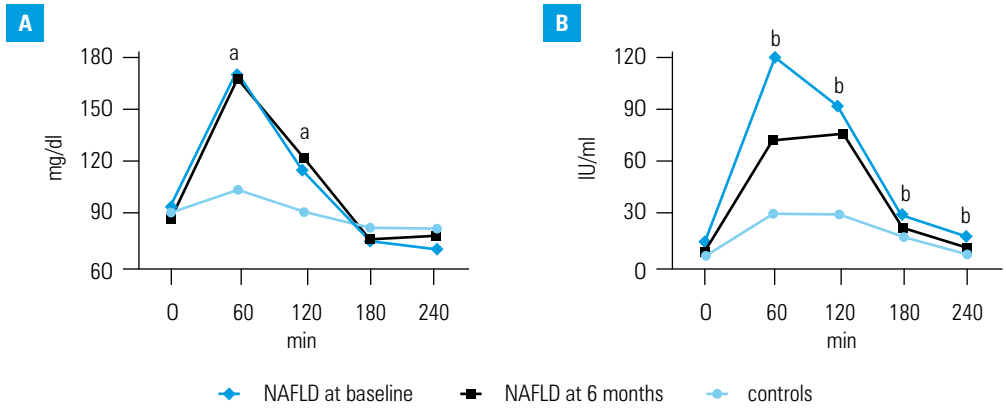


**FIGURE 2** Plasma glucose (panel A) and insulin (panel B) in subjects with nonalcoholic fatty liver disease (NAFLD) before and after 6 months of rosiglitazone treatment and in controls in the prolonged oral glucose tolerance test
**a** $P < 0.05$ vs. controls
**b** $P < 0.05$ for all NAFLD values vs. controls

**TABLE 2** Results of plasma glucose and insulin assays in the study group and controls

| | NAFLD subjects | | | | Controls |
|---|---|---|---|---|---|
| | baseline | 2 months | 4 months | 6 months | |
| glucose 0 min, mg/dl | 94 ±26 | 100 ±19 | 98 ±15 | 88 ±20 | 89 ±16 |
| glucose 60 min, mg/dl | 167 ±53 | – | – | 163 ±54 | 103 ±36[b] |
| glucose 120 min, mg/dl | 114 ±41 | – | – | 120 ±45 | 90 ±28[b] |
| glucose 180 min, mg/dl | 75 ±14 | – | – | 77 ±23 | 81 ±13 |
| glucose 240 min, mg/dl | 70 ±13 | – | – | 79 ±15 | 81 ±11 |
| insulin 0 min, IU/l | 15.9 ±6.7 | – | – | 9.2 ±7.3[a] | 10.2 ±7.9 |
| insulin 60 min, IU/l | 122.6 ±79.3 | – | – | 70.3 ±65.5[a] | 33.1 ±21.4[b] |
| insulin 120 min, IU/l | 97.8 ±76.2 | – | – | 73.3 ±82.0[a] | 34.1 ±44.7[b] |
| insulin 180 min, IU/l | 31.0 ±33.8 | – | – | 20.4 ±24.6[a] | 16.1 ±17.8[b] |
| insulin 240 min, IU/l | 15.9 ±18.3 | – | – | 12.0 ±10.2[a] | 6.8 ±6.2[b] |

a $P < 0.001$ vs. baseline
b $P < 0.05$ vs. all NAFLD values

Abbreviations: see **TABLE 1**

and observational studies,[22] since then treatment with rosiglitazone has been limited, and the latest EASD and ADA consensus statement no longer recommends its use.[23] It is worth noting, though, that this is not a universal view as, for instance, the Canadian Diabetes Association continues to consider rosiglitazone as a valuable antidiabetic agent and does not advise against its administration.[24]

Rosiglitazone effectively increases insulin sensitivity, which we confirmed in our NAFLD patients. Six months of daily treatment with 4 mg rosiglitazone resulted in a marked decrease in insulin resistance as measured with the HOMA index and a significant decrease in plasma insulin in the OGTT. Glucose control remained largely unchanged but because we included only nondiabetic patients, selective effect of rosiglitazone on insulin action, and not insulin secretion, has been confirmed. Moreover, rosiglitazone treatment led to a significant increase in adiponectin level, a potent anti-inflammatory and antiatherogenic cytokine.[25] However, plasma triglycerides after rosiglitazone therapy remained elevated, but this is a typical finding in type 2 diabetes patients treated with rosiglitazone.[26] Our findings are in agreement with other studies on rosiglitazone, including the most comprehensive prospective randomized FLIRT study. However, we have confirmed its significant insulin-sensitizing and liver-protective effects in nondiabetic subjects with NAFLD.[16,27-30]

Of note, despite a considerable effect of the drug on insulin sensitivity (HOMA index values were lowered to the same level as in controls), it failed to decrease plasma insulin to normal levels, and after the treatment period it still remained higher than in healthy controls. This observation confirms the limited effect that this drug can exert on obesity-related disorders,[30] which only proves that lifestyle modification in the treatment of NAFLD is indispensable.[31] However, any increase in insulin sensitivity is thought to be beneficial in terms of cardiovascular disease prevention;[32,33] therefore, our findings might have important implications, once confirmed by long-term studies.

Interestingly, we did not observe any adverse effects typically reported in other studies with rosiglitazone.[20,21,28-30] No patient reported edema or weight gain and the overall tolerance of the drug was very good. Although slight decrease in hematocrit was noted, it could hardly have any clinical relevance.

Apart from the decrease in insulin resistance, rosiglitazone also improved liver function: the enzymes decreased by 30% to 40% over 6 months. Rosiglitazone has been usually contraindicated in subjects with elevated liver enzymes, partly due to a serious adverse effect that troglitazone, the first thiazolidinedione in clinical use, had on the liver. However, in the case of rosiglitazone, this is an unjustified recommendation, as other studies also showed that it may improve liver function and markedly decrease elevated liver enzymes.[16,21,26-30]

Our study has several limitations. The number of subjects was relatively small, the follow-up period was only 6 months, and the study was an uncontrolled open-label trial. However, such design is the closest reflection of everyday clinical practice, while classic randomized placebo controlled trials have been increasingly criticized recently as being far from real-life conditions.[34] Another limitation is that we did not perform genetic studies to exclude hemochromatosis; however, the number of the studied subjects was so small that, considering the prevalence of the disease in Poland, it was highly unlikely that we would enroll an individual with iron overload.[35]

It should be noted that despite significant glucose-lowering, anti-inflammatory, and possible liver-protective effects, rosiglitazone use has been controversial. Controversy was mostly caused by an unclear association between rosiglitazone and the risk of myocardial infarction as well

as apparently higher risk of long-bone fracture in women. On September 23, 2010, the Food and Drug Agency limited its use in the United States, and the European Medicines Agency announced the suspension of the marketing authorizations for rosiglitazone-containing antidiabetic medicines in Europe a few months later. Nevertheless, considering our results, we conclude that rosiglitazone treatment in patients with NAFLD is safe, well-tolerated and leads to a significant improvement in the activity of liver function enzymes and insulin sensitivity, without adversely affecting plasma triglycerides. Long-term benefits of this therapy still remain to be established.

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ARTYKUŁ ORYGINALNY

# Rosiglitazon w leczeniu osób bez cukrzycy z niealkoholową stłuszczeniową chorobą wątroby

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**SŁOWA KLUCZOWE**

adiponektyna, insulinooporność, nietolerancja glukozy, rosiglitazon, stłuszczeniowa choroba wątroby

**STRESZCZENIE**

**WPROWADZENIE** Możliwości farmakoterapii niealkoholowej choroby stłuszczeniowej wątroby (*nonalcoholic fatty liver disease* – NAFLD) są ograniczone. Sugeruje się, że tiazolidinediony mogą mieć zastosowanie w leczeniu tej choroby.

**CELE** Przeprowadzono otwarte prospektywne badanie oceniające skuteczność i bezpieczeństwo rosiglitazonu w leczeniu pacjentów z NAFLD bez cukrzycy.

**PACJENCI I METODY** Grupa 27 pacjentów (średni wiek 44 ±11 lat, wskaźnik masy ciała 29,2 ±3,1 kg/m$^2$), z NAFLD potwierdzonym w biopsji wątroby, bez innych dolegliwości, otrzymywała rosiglitazon w dawce dobowej 4 mg przez 6 miesięcy

**WYNIKI** W trakcie 6 miesięcy stosowania rosiglitazonu nie wystąpiły żadne objawy niepożądane. Aktywność enzymów wątrobowych uległa stopniowemu i znamiennemu zmniejszeniu (aminotransferaza alaninowa z 101 ±59 do 58 ±39 IU/l, aminotransferaza asparaginianowa z 52 ±24 do 37 ±15 IU/l; $P$ <0,001). Stężenie insuliny w osoczu uległo również znamiennej redukcji o 30–50% w każdym punkcie czasowym doustnego testu obciążenia glukozą. Wskaźnik insulinooporności (*homeostatic model assessment index*) zmniejszył się z 3,73 ±1,89 do 2,06 ±1,68 ($P$ <0,001). Wartości glikemii nie uległy istotnej zmianie. Stężenie adiponektyny w osoczu wzrosło z 2198 ±1853 do 5734 ±1999 ng/ml ($P$ <0,001). Masa ciała, wartość hemoglobiny glikowanej $A_{1c}$, osoczowe stężenia lipidów i leptyny nie zmieniły się.

**WNIOSKI** Stosowanie rosiglitazonu u osób z NAFLD jest bezpieczne, dobrze tolerowane i prowadzi do znacznej poprawy czynności wątroby oraz insulinowrażliwości, bez niekorzystnego wpływu na profil lipidowy.

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